Disclosure: 02.035

SLWK No: 1427.008US1

PATENT APPLICATION

MODULATING IMMUNE RESPONSES

Inventors: LEON FERNANDO GARCIA-MARTINEZ, a citizen of Mexico, residing at 4926 214th Street S.E., in Woodinville, Washington, 98072;

YUCHING CHEN, a citizen of Taiwan, residing at 12737 97th Pl N.E., in Kirkland, Washington 98033; and

DAWN MICHELLE ANDREWS, a citizen of

MODULATING IMMUNE RESPONSES

This application is a continuation under 35 U.S.C. 111(a) of International Application No. PCT/US02/37738 filed November 21, 2002 and published in English as WO 03/045318 on June 5, 2003, which claimed priority under 35 U.S.C. 119(e) from U.S. Provisional Application SN 60/331958 filed November 21, 2001, which applications and publication are incorporated herein by reference.

This application also claims priority to U.S. Provisional Application Ser. No. 60/428,130 filed November 21, 2002 and U.S. Provisional Application Ser. No. 60/473,279 filed May 22, 2003 which are incorporate here by reference.

FIELD OF THE INVENTION

The invention relates to multimerized antibodies directed against the CD83 gene product, and methods of modulating the immune response of an animal by using such multimerized antibodies.

BACKGROUND OF THE INVENTION

CD83 is a 45 kilodalton glycoprotein that is predominantly expressed on the surface of dendritic cells and other cells of the immune system. Structural analysis of the predicted amino acid sequence of CD83 indicates that it is a member of the immunoglobulin superfamily. *See*, Zhou et al., J. Immunol. 149:735 (1992)). U.S. Patent 5,316,920 and WO 95/29236 disclose further information about CD83. While such information suggests that CD83 plays a role in the immune system, that role is undefined, and the interrelationship of CD83 with cellular factors remains unclear.

Moreover, treatment of many diseases could benefit from more effective methods for increasing or decreasing the immune response. Hence, new reagents and methods are needed for modulating the immune system through the CD83 gene and its gene product.

SUMMARY OF THE INVENTION

The invention provides methods for modulating an immune response. In one aspect, the invention relates to the surprising discovery that multimerized antibodies raised against the CD83 gene product can arrest cellular proliferation of immune cells. Hence, the invention provides a method of modulating the immune response by modulating the activity or expression of the CD83 gene products, for example, by using such multimerized antibodies.

Also according to the invention, the production of a cytokine such as interleukin-2, interleukin-4, or interlekin-10 can be modulated by modulating the activity or expression of a CD83 polypeptide. In some embodiments, a multimerized antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating granulocyte macrophage colony stimulating factor production in a mammal or in an immune cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody or a multimerized antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating tumor necrosis factor production in a mammal or in a mammalian cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody or a multimerized antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the mammalian cell can be contacted with the antibody. In some embodiments,

the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention further provides a method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody or a multimerized antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the human peripheral blood mononuclear cell can be contacted with the antibody.

The invention also provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein activated $CD4^+$ T-cells produce lower levels of interleukin-4 when the T-cells are contacted with the antibody. The invention further provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein $CD4^+$ T-cells proliferation is decreased when the T-cells are contacted with the antibody. The antibody can be a multimerized antibody. Such multimerized antibodies can be bound to a solid support, covalently crosslinked or bound together by a second entity such as a secondary antibody. Examples of antibodies of the invention include those that have an amino acid sequence that includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71 SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO: 94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98 or SEQ ID NO:99.

Nucleic acids encoding such an antibody can have, for example, a sequence that includes SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85 or SEQ ID NO:90.

The invention also provides a method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an antibody that comprises amino acid sequence includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71 SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO: 94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98 or SEQ ID NO:99. The antibody can be a multimerized antibody. The activity of a CD83 gene product can be decreased in a mammal or in a cell that is involved in an immune response, for example, a T cell.

The invention further provides a method for decreasing the translation of a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

In another embodiment, the invention provides a method for decreasing the translation of a CD83 gene product in a mammal, comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention further provides a method for decreasing proliferation of CD4+ T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71 SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO: 94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98 or SEQ ID NO:99. The antibody can be a multimerized antibody.

The invention also provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:67,

SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71 SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO: 94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98 or SEQ ID NO:99. The antibody can be a multimerized antibody.

The invention further provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments the interleukin-2 levels are decreased and the interleukin-4 levels are increased to treat an autoimmune disease. In other embodiments, the interleukin-2 levels are decreased and the interleukin-4 levels are increased to stimulate production of Th2-associated cytokines in transplant recipients, for example, to prolong survival of transplanted tissues.

The invention also provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71 SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID

NO: 94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98 or SEQ ID NO:99. The antibody can be a multimerized antibody.

The invention further provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments, the interleukin-10 levels are increased to treat neoplastic disease. In other embodiments, the interleukin-10 levels are increased to treat a tumor.

The invention also provides a method for increasing interleukin-2 levels in a mammal comprising administering to the mammal a functional CD83 polypeptide that comprises SEQ ID NO:9.

The invention further provides a method for increasing interleukin-2 levels in a mammal comprising: (a) transforming a T cell from the mammal with a nucleic acid encoding a functional CD83 polypeptide operably linked to a promoter functional in a mammalian cell, to generate a transformed T cell; (b) administering the transformed T cell to the mammal to provide increased levels of interleukin-2. In some embodiments, the CD83 polypeptide has a sequence that comprises SEQ ID NO:9 or the nucleic acid has a sequence that comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. Such methods for increasing interleukin-2 levels can be used to treat an allergy or an infectious disease.

The invention also provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

Such an antibody can have a sequence comprising includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47,

SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71 SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90; SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO: 94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:98 or SEQ ID NO:99. The antibody can be a multimerized antibody.

The invention further provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention also provides a method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide. In another embodiment, the invention provides a method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide. The CD83 polypeptide employed can, for example, have a sequence comprising SEQ ID NO:9.

Animals such as mammals and birds may be treated by the methods and compositions described herein. Such mammals and birds include humans, dogs, cats, and livestock, for example, horses, cattle, sheep, goats, chickens, turkeys and the like.

The invention further provides a mutant mouse that can serve as an animal model of diminished T cell activation or altered cytokine levels. The mutant mouse has an altered CD83 gene that produces a larger gene product, having SEQ ID NO:4 or containing SEQ ID NO:8. Also provided are methods of using the mutant mouse model to study the effects of cytokines on the immune system, inflammation, the function and regulation of CD83, T cell and dendritic cell activity, the immune response and conditions and treatments related thereto. Hence, the invention further provides a mutant mouse whose somatic and germ cells comprise a mutant CD83

gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of the mutant CD83 gene reduces CD4+T cell activation. The mutant CD83 gene can, for example, comprise SEQ ID NO:3.

The invention further provides a method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mouse having a mutant or wild type transgenic CD83 gene and observing whether CD4+ T cell activation is decreased or increased. The somatic and/or germ cells of the mutant mouse can comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. Alternatively, the somatic and/or germ cells of the mouse can contain a wild type CD83 gene, for example, SEQ ID NO:1 or SEQ ID NO:9.

The invention also provides a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. The invention further provides a mutant CD83 gene comprising nucleotide sequence SEQ ID NO:3.

DESCRIPTION OF THE FIGURES

Figure 1 summarizes flow cytometry data for G3 animals. As shown, reduced numbers of CD4+ T cells are seen in two animals from Pedigree 9, mouse 9.4.1 and mouse 9.4.9. All other animals analyzed on that day exhibit normal numbers of CD4+ T cells.

Figure 2 provides a graph of flow cytometry data for G3 animals that may have a mutant CD83 gene. Each diamond symbol represents an individual animal. As shown, multiple animals from the N2 generation exhibit a reduced percentage of CD4+ T cells.

Figure 3 provides the nucleotide sequence of wild type mouse CD83 (SEQ ID NO:1). The ATG start codon and the TGA stop codon are underlined.

Figure 4A-B provides the nucleotide sequence of the mutant CD83 gene (SEQ ID NO:3) of the invention derived from the mutant LCD4.1 animal. The ATG start codon, the mutation and the TGA stop codon are underlined.

Figure 5 provides the amino acid sequence for wild type (top, SEQ ID NO:2) and mutant (bottom, SEQ ID NO:4) CD83 coding regions. The additional C-terminal sequences arising because of the CD83 mutation are underlined.

Figure 6A illustrates that dendritic cells from wild type (?, WT DC) and mutant (¦ , mutant DC) mice are capable of the allogeneic activation of CD4+ T cells. CD4+ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation was measured by incorporation of tritiated thymidine.

Figure 6B illustrates that CD4+ T cells from mutant mice (¦ , mutant CD4) fail to respond to allogeneic stimulation with BALBc dendritic cells, although wild type animals (?, WT CD4+) respond normally. CD4+ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

Figure 7 provides a bar graph illustrating IL-2, IL-4, IL-5, TNFa, and IFN? production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 1 μg/ml of anti-CD3 antibodies and 0.2 μg/ml of anti-CD28 antibodies for 72 hours. As illustrated, IL-2 levels are lower, and IL-4 levels are higher in the CD83 mutant T cells.

Figure 8 provides a bar graph illustrating IL-10 production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 0.1 μg/ml of anti-CD28 antibodies and 1 to 10 μg/ml of anti-CD3 antibodies for 72 hours. As illustrated, IL-10 levels are higher in the CD83 mutant T cells.

Figure 9 provides a bar graph illustrating GM-CSF production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, GM-CSF production is higher in the CD83 mutant cells than in wild type cells.

Figure 10A provides a bar graph illustrating IL-4 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-4 mRNA levels are higher in the CD83 mutant cells.

Figure 10B provides a bar graph illustrating IL-10 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-10 mRNA levels are higher in the CD83 mutant cells.

Figure 11 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit IL-4 production in anti-CD3 and anti-CD28 antibody stimulated T cells. The amount of IL-4 produced by T cells in pg/ml is plotted versus the concentration of different anti-CD83 antibody preparations, including the 20B08 (?) anti-CD83 preparation, the 20D04 (¦) anti-CD83 preparation, the 14C12 (?) anti-CD83 preparation and the 11G05 (**X**) anti-CD83 antibody preparation.

Figure 12 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpms, which was used as an indicator of the amount of T cell proliferation, versus the concentration of the different anti-CD83 antibody preparations, including the 20D04 (?) anti-CD83 preparation, the 11G05 (¦) anti-CD83 antibody preparation, the 14C12 (?) anti-CD83 preparation and the 6G05 anti-CD83 preparation (**X**).

Figure 13 provides a graph illustrating that transgenic mice that over-express wild type CD83 have increased T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpms, which was used as an indicator of the amount of T cell proliferation, versus the concentration of OVA peptide. The transgenic mice utilized had a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide that can activate T-cells. When mixed with either transgenic or wild type dendritic cells in the presence of OVA peptide, transgenic CD4+ T cells had increased T-cell proliferation. However, transgenic dendritic cells could not substantially increase wild type CD4+ T cell proliferation. Transgenic CD83 CD4+ T cells mixed with wild type dendritic cells (?); transgenic CD83 CD4+ T cells mixed with transgenic dendritic cells (¦); wild type CD4+ T cells mixed with transgenic dendritic cells (?); and wild type CD4+ T cells mixed with wild type dendritic cells (**X**).

Figure 14 provides a schematic diagram of the structural elements included in the mouse CD83 protein used for generating antibodies.

Figure 15 provides a graph of ELISA data illustrating the titer obtained for different isolates of polyclonal anti-CD83 anti-sera. The first (?), second (¦) and third (?) isolates had similar titers, though the titer of the second isolate (¦) was somewhat higher.

Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein (?). Pre-immune serum (¦) had little effect on the proliferation of human PBMCs.

Figure 17A provides a sequence alignment of anti-CD83 heavy chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:52), 6G05H (SEQ ID NO:53), 20D04H (SEQ ID NO:54), 11G05 (SEQ ID NO:66) and 14C12 (SEQ ID NO:67) are provided. The CDR regions are highlighted in bold.

Figure 17B provides a sequence alignment of anti-CD83 light chain variable regions isolated by the invention. Sequences for isolates 20B08L (SEQ ID NO:55), 6G05L (SEQ ID NO:56), 20D04L (SEQ ID NO:57), 11G05L (SEQ ID NO:68) and 14C12L (SEQ ID NO:69) are provided. The CDR regions are highlighted in bold.

Figure 18 graphically illustrates that cells expressing CD83 can be detected and sorted using an anti-CD83 antibody preparation. In this study, a Hodgkin's lymphoma cell line, KMH2, and a commercially available anti-CD83 antibody preparation was used for FACS sorting.

Figure 19A-B shows that two antibody preparations of the invention can bind to endogenously produced human CD83, as detected by FACS sorting of KMH2 cells (see also Figure 18). Note that "Beer" is another name used for CD83.

Figure 20 illustrates that the 95F04 and 96G08 antibody preparations described herein can inhibit proliferation of human peripheral blood mononuclear cells as detected by [^{3}H] thymidine incorporation. As shown, when 30 μg/ml of the 95F04 (?) antibody preparation was present, incorporation of [^{3}H] thymidine dropped to about 2000 cpm. When 30 μg/ml 96G08 antibody preparation (?) was added to human peripheral blood mononuclear cells, [^{3}H] thymidine incorporation

was reduced to about 300 cpm. A third antibody preparation (98B11, ¦) provided slight inhibition of PBMC proliferation. These data indicate that the 95F04 and 96G08 antibody preparations can alter the function of human CD83 *in vivo*.

Figure 21 provides nucleotide and amino acid sequences for the monoclonal antibody 96G08 light chain.

Figure 22 provides nucleotide and amino acid sequences for the monoclonal antibody 96G08 heavy chain.

Figure 23 provides nucleotide and amino acid sequences for the monoclonal antibody 95F04 light chain.

Figure 24 provides nucleotide and amino acid sequences for the monoclonal antibody 95F04 heavy chain.

Figure 25A-B provides the results of one screen of anti-CD83 antibody preparations that were multimerized by binding them to microtiter plates. The plate-bound antibodies were screened for an ability to inhibit lymphocyte proliferation as measured by tritiated thymidine incorporation. As illustrated in Figure 25A many plate-bound anti-CD83 antibody preparations inhibit proliferation of activated lymphocytes, including the 94c09, 98a02, 94d08, 98d11, 101b08, 6g05, 20d04, 14c12, 11g05, 12g04, 32f12 and 98b11 preparations. Figure 25B further illustrates that some antibody preparations are highly effective inhibitors (e.g. 117G12) but others are not (e.g. 824pb and 98g08).

Figure 26 illustrates that the inhibitory activity of the multimerized (plate-bound) 6g05 antibody preparation is quenched by soluble mouse CD83 protein (mCD83rFc). Lymphocyte proliferation was measured by tritiated thymidine incorporation. As shown, the multimerized 6g05 antibody preparation is strongly inhibitory of proliferation when no CD83 protein is added. However, when the mouse CD83 protein is added to assay, little or no inhibition of lymphocyte proliferation is observed. The 98g08 antibody preparation was used as a negative control because it exhibited little or no lymphocyte inhibition in previous tests (see Figure 25B).

Figure 27 is a bar graph showing that both plate-bound and cross-linked 6g05 antibodies are highly effective inhibitors of lymphocyte proliferation.

Lymphocyte proliferation was measured by tritiated thymidine incorporation. As shown on the left side of the graph above "plate-bound" the presence of plate-bound 6g05 antibodies in the lymphocyte proliferation assay cause little tritiated thymidine incorporation (about 1000 cpm). Similarly, as shown on the right side of the graph above "1st Ab (1 μg/ml)" soluble cross-linked 6g05 antibodies also cause little tritiated thymidine incorporation (about 1800 cpm).

Figure 28 is a bar graph showing that several preparations of soluble cross-linked anti-CD83 antibodies are highly effective inhibitors of lymphocyte proliferation. Antibody preparations were cross-linked with the rabbit anti-mouse secondary antibody and lymphocyte proliferation was measured by tritiated thymidine incorporation. As shown, soluble cross-linked antibody preparations including the 6g05, 11g04, 12g04, 14c12, 20d04, 32f12, 94c09, 94d08, 98a02, 98d11(3), 101B08(2.7) and 117g12 preparations caused little tritiated thymidine incorporation.

Figure 29 shows that soluble, multimerized anti-CD83 antibodies exhibit inhibitory activity in mixed lymphocyte reaction assays. A series of anti-CD83 antibody preparations that were cross-linked using a rabbit anti-mouse antibody and then screened for inhibition of $CD4^+$ T cellular proliferation after activation of the $CD4^+$ T cells with CD11 cells in a mixed lymphocyte reaction assay. As shown, the 98a02, 98d11, 20d04, 14c12, 12g04, and 117g12 inhibit lymphocyte proliferation in this assay.

Figure 30 shows that many anti-CD83 antibody preparations can inhibit the recall response of lymphocytes. BALBc mice were first immunized with keyhole limpet hemocyanin (KLH) prior to spleen removal and CD11c and CD4+ cell isolation. CD11c and CD4+ cells were mixed and added to microtiter wells coated with anti-CD83 antibodies. Lymphocyte proliferation was measured by tritiated thymidine incorporation. As shown, the 94c09, 98a02, 6g05, 20d04, and 117104 antibody preparations inhibited proliferation of activated lymphocytes exposed to an antigen (KLH) to which they had been immunized.

Figure 31A-B shows that soluble but cross-linked 6g05 and 14c12 anti-CD83 antibody preparations not only inhibit activated lymphocyte cell proliferation

(Figure 31B) but also have very low caspase activity (Figure 31A). Caspase activity was determined using a fluorogenic substrate and plotted as relative fluorescent units (RFU) on the y axis.

Figure 32 shows that the percentage of activated lymphocytes that express annexinV is reduced after treatment with soluble but cross-linked 6g05 and 14c12 anti-CD83 antibody preparations.

Figure 33 shows that the activation marker CD69 is expressed on splenocytes that were activated with Concavalin A and exposed to anti-CD83 antibodies. The anti-CD83 antibodies employed were the 6g05, 14c12, 98b11 and 112d08 anti-CD83 antibody preparations that were shown to inhibit activated splenocyte proliferation.

Figure 34A-E shows that a population of activated splenocytes mixed with anti-CD83 antibody preparations have lost the blasting (dividing) cells as detected by FACS sorting. The antibody preparations employed were the rabbit anti-mouse antibody, called the 2^{nd} Ab (Figure 34A), the 6g05 antibody preparation (Figure 34B), the 98b11 antibody preparation (Figure 34C), the 14c12 antibody preparation (Figure 34D), and the 112d08 antibody preparation (Figure 34E). Almost all cells exposed to the 6g05 or 98b11 antibody preparations sort as small cells with a 2N content of DNA as illustrated by the high proportion of cells towards the left (smaller) side of the population distribution compared to cells exposed to the control 2^{nd} Ab, 14c12 and 112d08 preparations in Figures 34A, C and E.

Figure 35A shows that the proportion of cells in the G1/G0 phase of the cell cycle is increased when a population of activated splenocytes is treated with anti-CD83 antibody preparations. The antibody preparations employed were the control rabbit anti-mouse antibody, called the 2^{nd} Ab, the 6g05 antibody preparation, the 14c12 antibody preparation, and the negative control 112d08 antibody preparation. Both of the 6g05 and 14c12 antibody preparations arrest the activated splenocytes in the G1/G0 phase of the cell cycle.

Figure 35B shows the proportion of cells in the G2/M phase of the cell cycle after a population of activated splenocytes is treated with anti-CD83 antibody preparations. The antibody preparations employed were the control rabbit anti-

mouse antibody, called the 2nd Ab, the 6g05 antibody preparation, the 14c12 antibody preparation, and the negative control 112d08 antibody preparation.

Figure 35C shows that the proportion of cells in the S phase of the cell cycle is decreased when a population of activated splenocytes is treated with anti-CD83 antibody preparations. The antibody preparations employed were the control rabbit anti-mouse antibody, called the 2nd Ab, the 6g05 antibody preparation, the 14c12 antibody preparation, and the negative control 112d08 antibody preparation. Activated splenocytes treated with either of the 6g05 or 14c12 antibody preparations have lesser numbers of cells in the S phase of the cell cycle.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods for modulating the immune system. For example, according to the invention, loss or reduction of CD83 activity *in vivo* results in decreased numbers of immune cells, for example, decreased numbers of T cells. In some embodiments, binding entities such as monoclonal antibodies that are capable of inhibiting the function of CD83 are provided for use in the invention. In other embodiments the binding entities or antibodies are multimerized. The compositions and methods of the invention can be used for treating conditions involving an inappropriate immune response, for example, autoimmune diseases, inflammation, tissue rejection, arthritis, atherosclerosis and the like.

CD83

CD83 is a lymphocyte and dendritic cell activation antigen that is expressed by activated lymphocytes and dendritic cells. CD83 is also a single-chain cell-surface glycoprotein with a molecular weight of about 45,000 that is believed to be a member of the Ig superfamily. The structure predicted from the CD83 amino acid sequence indicates that CD83 is a membrane glycoprotein with a single extracellular Ig-like domain, a transmembrane domain and cytoplasmic domain of approximately forty amino acids. The mature CD83 protein has about 186 amino acids and is composed of a single extracellular V type immunoglobulin (Ig)-like domain, a transmembrane domain and a thirty nine amino acid cytoplasmic domain. Northern

blot analysis has revealed that CD83 is translated from three mRNA transcripts of about 1.7, 2.0 and 2.5 kb that are expressed by lymphoblastoid cell lines. It is likely that CD83 undergoes extensive post-translational processing because CD83 is expressed as a single chain molecule, but the determined molecular weight is twice the predicted size of the core protein. *See* U.S. Patent 5,766,570.

An example of a human CD83 gene product that can be used in the invention is provided below (SEQ ID NO:9):

```
  1 MSRGLQLLLL SCAYSLAPAT PEVKVACSED VDLPCTAPWD
 41 PQVPYTVSWV KLLEGGEERM ETPQEDHLRG QHYHQKGQNG
 81 SFDAPNERPY SLKIRNTTSC NSGTYRCTLQ DPDGQRNLSG
121 KVILRVTGCP AQRKEETFKK YRAEIVLLLA LVIFYLTLII
161 FTCKFARLQS IFPDFSKAGM ERAFLPVTSP NKHLGLVTPH
201 KTELV
```

Such a CD83 gene product can be encoded by a number of different nucleic acids. One example of a human CD83 nucleic acid is provided below (SEQ ID NO:10).

```
  1 CCTGGCGCAG CCGCAGCAGC GACGCGAGCG AACTCGGCCG
 41 GGCCCGGGCG CGCGGGGGCG GGACGCGCAC GCGGCGAGGG
 81 CGGCGGGTGA GCCGGGGGCG GGGACGGGGG CGGGACGGGG
121 GCGAAGGGGG CGGGGACGGG GGCGCCCGCC GGCCTAACGG
161 GATTAGGAGG GCGCGCCACC CGCTTCCGCT GCCCGCCGGG
201 GAATCCCCCG GGTGGCGCCC AGGGAAGTTC CCGAACGGGC
241 GGGCATAAAA GGGCAGCCGC GCCGGCGCCC CACAGCTCTG
281 CAGCTCGTGG CAGCGGCGCA GCGCTCCAGC CATGTCGCGC
321 GGCCTCCAGC TTCTGCTCCT GAGCTGCGCC TACAGCCTGG
361 CTCCCGCGAC GCCGGAGGTG AAGGTGGCTT GCTCCGAAGA
401 TGTGGACTTG CCCTGCACCG CCCCCTGGGA TCCGCAGGTT
441 CCCTACACGG TCTCCTGGGT CAAGTTATTG GAGGGTGGTG
481 AAGAGAGGAT GGAGACACCC CAGGAAGACC ACCTCAGGGG
521 ACAGCACTAT CATCAGAAGG GGCAAAATGG TTCTTTCGAC
561 GCCCCCAATG AAAGGCCCTA TTCCCTGAAG ATCCGAAACA
601 CTACCAGCTG CAACTCGGGG ACATACAGGT GCACTCTGCA
```

641 GGACCCGGAT GGGCAGAGAA ACCTAAGTGG CAAGGTGATC

681 TTGAGAGTGA CAGGATGCCC TGCACAGCGT AAAGAAGAGA

721 CTTTTAAGAA ATACAGAGCG GAGATTGTCC TGCTGCTGGC

761 TCTGGTTATT TTCTACTTAA CACTCATCAT TTTCACTTGT

801 AAGTTTGCAC GGCTACAGAG TATCTTCCCA GATTTTTCTA

841 AAGCTGGCAT GGAACGAGCT TTTCTCCCAG TTACCTCCCC

881 AAATAAGCAT TTAGGGCTAG TGACTCCTCA CAAGACAGAA

921 CTGGTATGAG CAGGATTTCT GCAGGTTCTT CTTCCTGAAG

961 CTGAGGCTCA GGGGTGTGCC TGTCTGTTAC ACTGGAGGAG

1001 AGAAGAATGA GCCTACGCTG AAGATGGCAT CCTGTGAAGT

1041 CCTTCACCTC ACTGAAAACA TCTGGAAGGG GATCCCACCC

1081 CATTTTCTGT GGGCAGGCCT CGAAAACCAT CACATGACCA

1121 CATAGCATGA GGCCACTGCT GCTTCTCCAT GGCCACCTTT

1161 TCAGCGATGT ATGCAGCTAT CTGGTCAACC TCCTGGACAT

1201 TTTTTCAGTC ATATAAAAGC TATGGTGAGA TGCAGCTGGA

1241 AAAGGGTCTT GGGAAATATG AATGCCCCCA GCTGGCCCGT

1281 GACAGACTCC TGAGGACAGC TGTCCTCTTC TGCATCTTGG

1321 GGACATCTCT TTGAATTTTC TGTGTTTTGC TGTACCAGCC

1361 CAGATGTTTT ACGTCTGGGA GAAATTGACA GATCAAGCTG

1401 TGAGACAGTG GGAAATATTT AGCAAATAAT TTCCTGGTGT

1441 GAAGGTCCTG CTATTACTAA GGAGTAATCT GTGTACAAAG

1481 AAATAACAAG TCGATGAACT ATTCCCCAGC AGGGTCTTTT

1521 CATCTGGGAA AGACATCCAT AAAGAAGCAA TAAAGAAGAG

1561 TGCCACATTT ATTTTTATAT CTATATGTAC TTGTCAAAGA

1601 AGGTTTGTGT TTTTCTGCTT TTGAAATCTG TATCTGTAGT

1641 GAGATAGCAT TGTGAACTGA CAGGCAGCCT GGACATAGAG

1681 AGGGAGAAGA AGTCAGAGAG GGTGACAAGA TAGAGAGCTA

1721 TTTAATGGCC GGCTGGAAAT GCTGGGCTGA CGGTGCAGTC

1761 TGGGTGCTCG CCCACTTGTC CCACTATCTG GGTGCATGAT

1801 CTTGAGCAAG TTCCTTCTGG TGTCTGCTTT CTCCATTGTA

1841 AACCACAAGG CTGTTGCATG GGCTAATGAA GATCATATAC

1881 GTGAAAATTA TTTGAAAACA TATAAAGCAC TATACAGATT

```
1921 CGAAACTCCA TTGAGTCATT ATCCTTGCTA TGATGATGGT
1961 GTTTTGGGGA TGAGAGGGTG CTATCCATTT CTCATGTTTT
2001 CCATTGTTTG AAACAAAGAA GGTTACCAAG AAGCCTTTCC
2041 TGTAGCCTTC TGTAGGAATT CTTTTGGGGA AGTGAGGAAG
2081 CCAGGTCCAC GGTCTGTTCT TGAAGCAGTA GCCTAACACA
2121 CTCCAAGATA TGGACACACG GGAGCCGCTG GCAGAAGGGA
2161 CTTCACGAAG TGTTGCATGG ATGTTTTAGC CATTGTTGGC
2201 TTTCCCTTAT CAAACTTGGG CCCTTCCCTT CTTGGTTTCC
2241 AAAGGCATTT ATTGCTGAGT TATATGTTCA CTGTCCCCCT
2281 AATATTAGGG AGTAAAACGG ATACCAAGTT GATTTAGTGT
2321 TTTTACCTCT GTCTTGGCTT TCATGTTATT AAACGTATGC
2361 ATGTGAAGAA GGGTGTTTTT CTGTTTTATA TTCAACTCAT
2401 AAGACTTTGG GATAGGAAAA ATGAGTAATG GTTACTAGGC
2441 TTAATACCTG GGTGATTACA TAATCTGTAC AACGAACCCC
2481 CATGATGTAA GTTTACCTAT GTAACAAACC TGCACTTATA
2521 CCCATGAACT TAAAATGAAA GTTAAAAATA AAAAACATAT
2561 ACAAATAAAA AAAA
```

A sequence of a wild type mouse CD83 gene that can be used in the invention is provided herein as SEQ ID NO:1. SEQ ID NO:1 is provided below with the ATG start codon and the TGA stop codon identified by underlining.

```
   1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT
  41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC
  81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC
 121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG
 161 TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
 201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC
 241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC
 281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC
 321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA
 361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
```

401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG

441 TTGTTTTCTA CCTGACACTC ATCATTTTCA CCTGCAAATT

481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT

521 GGTACGGAAC AAGCTTTTCT TCCAGTCACC TCCCCAAGCA

561 AACATTTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT

601 A**TGA**GTAGGA TCTCCACTGG TTTTTACAAA GCCAAGGGCA

641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA

681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT

721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA

761 GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA

801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG

841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC

881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA

921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG

961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA

1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC

1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA

1081 TATTTAGCAA ATAATTTCCC AGTGCGAAGG TCCTGCTATT

1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT

1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA

1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT

1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG

1281 TTTTTTCAAA GAAGTGTGTT TCTTTCCTTT TTTAAAATAT

1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC

1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA

1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA

1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC

1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TTCACTCTCT

1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT

1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA

1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT

1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT

```
1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT
1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG
1761 AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG
1841 ACAGGAGGAA GTTCTCAGAT GTTGCATTGA TGTAACATTG
1881 TTGCATTTCT TTAATGAGCT GGGCTCCTTC CTCATTTGCT
1921 TCCCAAAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC
1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA
2041 ATGCATGTGA A
```

Nucleic acids having SEQ ID NO:1 encode a mouse polypeptide having SEQ ID NO:2, provided below.

```
  1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA
 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTGC
121 PKEATESTFR KYRAEAVLLF SLVVFYLTLI IFTCKFARLQ
161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV
```

According to the invention, loss or reduction of CD83 activity *in vivo* results in a decreased immune response, for example, decreased numbers of T cells. The effect of CD83 on the immune response was initially ascertained through use of a mutant mouse that encodes a mutant CD83. Such a mutant mouse has a CD83 gene encoding SEQ ID NO:4, with added C-terminal sequences provided by SEQ ID NO:8. In contrast to these wild type CD83 nucleic acids and polypeptides, the mutant CD83 gene of the invention has SEQ ID NO:3. SEQ ID NO:3 is provided below with the ATG start codon, the mutation, and the TGA stop codon are identified by underlining.

```
  1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT
 41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC
 81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC
```

121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG

161 TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG

201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC

241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC

281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC

321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA

361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC

401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG

441 TTGTTTTCTA CCTGACACTC ATCATTTTCA CCTGCAAATT

481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT

521 GGTACGGAAC AAGCTTTTCT TCCAGTCACC TCCCCAAGCA

561 AACATTTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT

601 A**A**GAGTAGGA TCTCCACTGG TTTTTACAAA GCCAAGGGCA

641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA

681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT

721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA

761 GGGTCT**TGA**G CACCATCATA TGATCACGAA GCATGGAGTA

801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG

841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC

881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA

921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG

961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA

1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC

1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA

1081 TATTTAGCAA ATAATTTCCC AGTGCGAAGG TCCTGCTATT

1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT

1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA

1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT

1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG

1281 TTTTTTCAAA GAAGTGTGTT TCTTTCCTTT TTTAAAATAT

1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC

1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA

```
1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA
1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC
1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TTCACTCTCT
1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT
1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT
1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT
1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT
1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG
1761 AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG
1841 ACAGGAGGAA GTTCTCAGAT GTTGCATTGA TGTAACATTG
1881 TTGCATTTCT TTAATGAGCT GGGCTCCTTC CTCATTTGCT
1921 TCCCAAAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC
1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA
2041 ATGCATGTGA A
```

The change from a thymidine in SEQ ID NO:1 to an adenine in SEQ ID NO:3 at the indicated position (602) leads to read-through translation because the stop codon at positions 602-604 in SEQ ID NO:1 is changed to a codon that encodes an arginine. Accordingly, mutant CD83 nucleic acids having SEQ ID NO:3 encode an elongated polypeptide having SEQ ID NO:4, provided below, where the extra amino acids are underlined.

```
  1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA
 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTGC
121 PKEATESTFR KYRAEAVLLF SLVVFYLTLI IFTCKFARLQ
161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETVRVGS
201 PLVFTKPRAH QISVPECHPD KRRMSSILRW QPFFEVLHLT
241 VGSTLLPDTG S
```

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:5.

```
  1  ATGTCGCAAG GCCTCCAGCT CCTGTTTCTA GGCTGCGCCT
 41  GCAGCCTGGC ACCCGCGATG GCGATGCGGG AGGTGACGGT
 81  GGCTTGCTCC GAGACCGCCG ACTTGCCTTG CACAGCGCCC
121  TGGGACCCGC AGCTCTCCTA TGCAGTGTCC TGGGCCAAGG
161  TCTCCGAGAG TGGCACTGAG AGTGTGGAGC TCCCGGAGAG
201  CAAGCAAAAC AGCTCCTTCG AGGCCCCCAG GAGAAGGGCC
241  TATTCCCTGA CGATCCAAAA CACTACCATC TGCAGCTCGG
281  GCACCTACAG GTGTGCCCTG CAGGAGCTCG GAGGGCAGCG
321  CAACTTGAGC GGCACCGTGG TTCTGAAGGT GACAGGATGC
361  CCCAAGGAAG CTACAGAGTC AACTTTCAGG AAGTACAGGG
401  CAGAAGCTGT GTTGCTCTTC TCTCTGGTTG TTTTCTACCT
441  GACACTCATC ATTTTCACCT GCAAATTTGC ACGACTACAA
481  AGCATTTTCC CAGATATTTC TAAACCTGGT ACGGAACAAG
521  CTTTTCTTCC AGTCACCTCC CCAAGCAAAC ATTTGGGGCC
561  AGTGACCCTT CCTAAGACAG AAACGGTAAG AGTAGGATCT
601  CCACTGGTTT TTACAAAGCC AAGGGCACAT CAGATCAGTG
641  TGCCTGAATG CCACCCGGAC AAGAGAAGAA TGAGCTCCAT
681  CCTCAGATGG CAACCTTTCT TTGAAGTCCT TCACCTGACA
721  GTGGGCTCCA CACTACTCCC TGACACAGGG TCTTGA
```

Nucleic acids having SEQ ID NO:5 also encode a polypeptide having SEQ ID NO:4.

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:7.

```
  1  AGAGTAGGAT CTCCACTGGT TTTTACAAAG CCAAGGGCAC
 41  ATCAGATCAG TGTGCCTGAA TGCCACCCGG ACAAGAGAAG
```

```
 81  AATGAGCTCC ATCCTCAGAT GGCAACCTTT CTTTGAAGTC
121  CTTCACCTGA CAGTGGGCTC CACACTACTC CCTGACACAG
161  GGTCTTGA
```

The invention also provides a mutant CD83 containing SEQ ID NO:8, provided below.

```
  1  RVGSPLVFTK PRAHQISVPE CHPDKRRMSS ILRWQPFFEV
 41  LHLTVGSTLL PDTGS
```

SEQ ID NO:8 contains read through sequences that are not present in the wild type CD83 polypeptide but are present in the mutant CD83 gene product provided by the invention.

In some embodiments, the CD83 gene product is used for generating antibodies. While any of the CD83 gene products described herein can be employed for immunization of animal, in some embodiments the extracellular Ig-like domain of the CD83 gene product is used for immunization, or antibodies are screened for reactivity with the extracellular Ig-like domain. The extracellular Ig-like domain of the human CD83 gene product spans amino acids 21-127, and is provided below (SEQ ID NO:97):

```
 21                          PEVKVACSED VDLPCTAPWD
 41 PQVPYTVSWV KLLEGGEERM ETPQEDHLRG QHYHQKGQNG
 81 SFDAPNERPY SLKIRNTTSC NSGTYRCTLQ DPDGQRNLSG
121 KVILRVT
```

CD83 Antibodies

The invention provides antibody preparations directed against the mutant and wild type CD83 polypeptides of the invention, for example, against a polypeptide having SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9. Other antibodies of interest can bind to the cytoplasmic tail of CD83.

In some embodiments, the anti-CD83 antibodies are multimerized antibodies. According to the invention, multimerized anti-CD83 antibodies are

surprisingly effective inhibitors of lymphocyte cell proliferation. As used herein, an "multimerized" anti-CD83 antibody is a collection of anti-CD83 antibodies that are in close proximity. While such multimerized antibodies can be covalently linked, no such covalent linkage is necessary. Instead, multimerization of anti-CD83 antibodies can simply involve bringing the antibodies into close proximity, for example, by attachment to a solid support such as a plate or a bead. Alternatively, the antibodies can be non-covalently linked together through another entity, for example, any convenient non-covalent binding entity or secondary antibody. Hence, any available means for bringing the anti-CD83 antibodies into proximity can be used to generate the multimerized antibodies of the invention.

In some embodiments, the anti-CD83 binding proteins or antibodies can be chemically cross-linked or genetically fused with any available crosslinking reagent. Crosslinking can be achieved using one or a combination of a wide variety of multifunctional reagents. Such crosslinking agents include glutaraldehyde, succinaldehyde, octanedialdehyde and glyoxal. Additional multifunctional crosslinking agents include halo-triazines, e.g., cyanuric chloride; halo-pyrimidines, e.g., 2,4,6-trichloro/bromo-pyrimidine; anhydrides or halides of aliphatic or aromatic mono- or di-carboxylic acids, e.g., maleic anhydride, (meth)acryloyl chloride, chloroacetyl chloride; N-methylol compounds, e.g., N-methylol-chloro acetamide; di-isocyanates or di-isothiocyanates, e.g., phenylene-1,4-di-isocyanate and aziridines. Other crosslinking agents include epoxides, such as, for example, di-epoxides, tri-epoxides and tetra-epoxides. Other crosslinking agents include, for example, dimethyl 3, 3'-dithiobispropionimidate-HCl (DTBP); dithiobis (succinimidylpropionate) (DSP); bismaleimidohexane (BMH); bis[Sulfosuccinimidyl]suberate (BS); 1,5-difluoro-2,4-dinitrobenzene (DFDNB); dimethylsuberimidate-2HCl (DMS); disuccinimidyl glutarate (DSG); disulfosuccinimidyl tartarate (Sulfo-DST); 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC); ethylene glycolbis [sulfo-succinimidylsuccinate] (Sulfo-EGS); N-[?-maleimido-butyryloxy]succinimide ester (GMBS); N-hydroxysulfosuccinimidyl-4-azidobenzoate (Sulfo-HSAB); sulfosuccinimidyl-6-[a-methyl-a-(2-pyridyldithio) toluamido]hexanoate (Sulfo-LC-

SMPT); bis-[ß-(4-azidosalicylamido) ethyl]disulfide (BASED); and NHS-PEG-Vinylsulfone (NHS-PEG-VS).

In some embodiments, crosslinkers useful with various preparations of anti-CD83 antibodies of this invention include (1) those which create covalent links from one cysteine side chain of a protein to another cysteine side chain, (2) those which create covalent links from one lysine side chain of a protein to another, or (3) those which create covalent links from one cysteine side chain of a protein to a lysine side chain.

In other embodiments, the anti-CD83 antibodies are reversibly crosslinked. Such reversibly crosslinked antibodies are useful for short term use, for example, for short term control of the immune response either in vivo or in vitro, or for controlled dissipation of the anti-CD83 antibodies at a localized site after administration for short term therapeutic purposes. Examples of reversible crosslinkers are described in T. W. Green, Protective Groups in Organic Synthesis, John Wiley & Sons (Eds.) (1981). Other types of reversible crosslinkers are disulfide bond-containing crosslinkers. The crosslinks formed by such crosslinkers can be broken by the addition of reducing agent, such as cysteine, to the environment of the crosslinked anti-CD83 antibodies. Disulfide crosslinkers are described in the Pierce Catalog and Handbook (1994-1995).

Examples of crosslinkers that may be used also include: Homobifunctional (Symmetric); DSP -- Dithiobis(succinimidylpropionate), also know as Lomant,'s Reagent; DTSSP -- 3-3'-Dithiobis (sulfosuccinimidyl-propionate), water soluble version of DSP; DTBP -- Dimethyl 3,3'-dithiobispropionimidate-HCl; BASED -- Bis-(ß-[4-azidosalicylamido] ethyl)disulfide; DPDPB --1,4-Di-(3'-[2'-pyridyldithio]-propionamido)butane; Heterobifunctional (Asymmetric); SPDP -- N-Succinimidyl-3-(2-pyridyldithio)propionate; LC-SPDP -- Succinimidyl-6-(3-[2-pyridyldithio] propionate)hexanoate; Sulfo-LC-SPDP -- Sulfosuccinimidyl-6-(3-[2-pyridyldlthio] propionate)hexanoate, water soluble version of LC-SPDP; APDP -- N-(4-[p-azidosalicylamido]butyl)-3'-(2'-pyridyldithio) propionamide; SADP--N-Succinimidyl(4-azidophenyl)1,3'-dithiopropionate; Sulfo-SADP -- Sulfosuccinimidyl(4-azidophenyl) 1,3'-dithiopropionate, water soluble version of

SADP; SAED -- Sulfosuccinimidyl-2-(7-azido-4-methycoumarin-3-acetamide)ethyl-1,3'dithiopropionate; SAND -- Sulfosuccinimidyl-2-(m-azido-o-nitrobenzamido)ethyl-1,3'-dithiopropionate; SASD -- Sulfosuccinimidyl-2-(p-azidosalicylamido)ethyl-1,3'-dithiopropionate; SMPB -- Succinimidyl-4-(p-maleimidophenyl)butyrate; Sulfo-SMPB -- Sulfosuccinimidyl-4-(p-maleimidophenyl)butyrate; SMPT -- 4-Succinimidyloxycarbonyl-methyl-a-(2-pyridylthio) toluene; Sulfo-LC-SMPT -- Sulfosuccinimidyl-6-(a-methyl-a-(2-pyridylthio)toluamido)hexanoate.

In another embodiment, a fusion protein can be made with a selected anti-CD83 antibody to allow a domain to be attached to one or both of the polypeptides comprising the anti-CD83 antibody to be bound to a solid substrate. For example, glutathione-S-transferase/anti-CD83 fusion proteins can be linked to another anti-CD83 preparation having glutathione attached thereto or the glutathione-S-transferase/anti-CD83 fusion proteins can be adsorbed onto a solid support having glutathione attached thereto, such as glutathione sepharose beads (Sigma Chemical, St. Louis, Mo.) or glutathione derivatized microtiter plate. In another embodiment, DSP-crosslinked antibodies can be linked to protein G agarose beads. Other techniques for immobilizing polypeptides on solid support materials can also be used. For example, an anti-CD83 antibody can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated anti-CD83 polypeptides can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized with a streptavidin-linked antiCD83 antibody preparation, streptavidin-coated beads or another solid support material.

Therefore, in one embodiment, the invention provides antibodies capable of reducing CD83 activity and decreasing an immune response in a mammal. Such antibodies can be multimerized antibodies. These antibodies may be used as CD83 inhibitory agents in the methods of the invention as described herein. In another embodiment, the antibodies of the invention can activate CD83 activity. Such activating antibodies may be used as CD83 stimulatory agents.

All antibody molecules belong to a family of plasma proteins called immunoglobulins, whose basic building block, the immunoglobulin fold or domain, is used in various forms in many molecules of the immune system and other biological recognition systems. A typical immunoglobulin has four polypeptide chains, containing an antigen binding region known as a variable region and a non-varying region known as the constant region.

Native antibodies and immunoglobulins are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains (Clothia et al., J. Mol. Biol. 186, 651-66, 1985); Novotny and Haber, Proc. Natl. Acad. Sci. USA 82, 4592-4596 (1985).

Depending on the amino acid sequences of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are at least five (5) major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG-1, IgG-2, IgG-3 and IgG-4; IgA-1 and IgA-2. The heavy chains constant domains that correspond to the different classes of immunoglobulins are called alpha (a), delta (d), epsilon (e), gamma (?) and mu (μ), respectively. The light chains of antibodies can be assigned to one of two clearly distinct types, called kappa (?) and lambda (?), based on the amino sequences of their constant domain. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "variable" in the context of variable domain of antibodies, refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies. The variable domains are for binding and determine the specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed through the variable domains of antibodies. It is concentrated in three segments called complementarity determining regions (CDRs) also known as hypervariable regions both in the light chain and the heavy chain variable domains.

The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a ß-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the ß-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector function, such as participation of the antibody in antibody-dependent cellular toxicity.

An antibody that is contemplated for use in the present invention thus can be in any of a variety of forms, including a whole immunoglobulin, an antibody fragment such as Fv, Fab, and similar fragments, a single chain antibody that includes the variable domain complementarity determining regions (CDR), and the like forms, all of which fall under the broad term "antibody," as used herein. Moreover, the multimerized antibodies of the invention can be an aggregation or multimerization of whole immunoglobulins. Alternatively, the multimerized antibodies of the invention can be an aggregation or multimerization of antibody fragments such as Fv, Fab, single chain antibodies that include the variable domain complementarity determining regions (CDR), CDRs and the like. Such intact antibodies or antibody fragments can be multimerized by any convenient means, including covalent linkage or non-covalent association.

The present invention contemplates the use of any specificity of an antibody, polyclonal or monoclonal, and is not limited to antibodies that recognize and

immunoreact with a specific epitope. In preferred embodiments, in the context of both the therapeutic and screening methods described below, an antibody or fragment thereof is used that is immunospecific for an extracellular portion of the CD83 protein.

The term "antibody fragment" refers to a portion of a full-length antibody, generally the antigen binding or variable region. Examples of antibody fragments include Fab, Fab', $F(ab')_2$ and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen binding fragments, which are capable of cross-linking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from antibody fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and $F(ab')_2$ fragments.

Antibody fragments retain some ability to selectively bind with its antigen or receptor and are defined as follows:

(1) Fab is the fragment that contains a monovalent antigen-binding fragment of an antibody molecule. A Fab fragment can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain.

(2) Fab' is the fragment of an antibody molecule can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per antibody molecule. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

(3) $(Fab')_2$ is the fragment of an antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction. $F(ab')_2$ is a dimer of two Fab' fragments held together by two disulfide bonds.

(4) Fv is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (V_H -V_L dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V_H -V_L dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

(5) Single chain antibody ("SCA"), defined as a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Such single chain antibodies are also referred to as "single-chain Fv" or "sFv" antibody fragments. Generally, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds. Springer-Verlag, N.Y., pp. 269-315 (1994).

The term "diabodies" refers to a small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161, and Hollinger et al., Proc. Natl. Acad Sci. USA 90: 6444-6448 (1993).

The preparation of polyclonal antibodies is well-known to those skilled in the art. See, for example, Green, et al., Production of Polyclonal Antisera, in: Immunochemical Protocols (Manson, ed.), pages 1-5 (Humana Press); Coligan, et al., Production of Polyclonal Antisera in Rabbits, Rats Mice and Hamsters, in:

Current Protocols in Immunology, section 2.4.1 (1992), which are hereby incorporated by reference.

The preparation of monoclonal antibodies likewise is conventional. See, for example, Kohler & Milstein, Nature, 256:495 (1975); Coligan, et al., sections 2.5.1-2.6.7; and Harlow, et al., in: Antibodies: A Laboratory Manual, page 726 (Cold Spring Harbor Pub. (1988)), which are hereby incorporated by reference. Methods of *in vitro* and *in vivo* manipulation of monoclonal antibodies are also available to those skilled in the art. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, Nature 256, 495 (1975), or they may be made by recombinant methods, for example, as described in U.S. Patent No. 4,816,567. The monoclonal antibodies for use with the present invention may also be isolated from antibody libraries using the techniques described in Clackson et al. Nature 352: 624-628 (1991), as well as in Marks et al., J. Mol Biol. 222: 581-597 (1991).

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, e.g., Coligan, et al., sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; Barnes, et al., Purification of Immunoglobulin G (IgG), in: Methods in Molecular Biology, Vol. 10, pages 79-104 (Humana Press (1992).

Another method for generating antibodies involves a Selected Lymphocyte Antibody Method (SLAM). The SLAM technology permits the generation, isolation and manipulation of monoclonal antibodies without the process of hybridoma generation. The methodology principally involves the growth of antibody forming cells, the physical selection of specifically selected antibody forming cells, the isolation of the genes encoding the antibody and the subsequent cloning and expression of those genes.

More specifically, an animal is immunized with a source of specific antigen. The animal can be a rabbit, mouse, rat, or any other convenient animal. This immunization may consist of purified protein, in either native or recombinant form, peptides, DNA encoding the protein of interest or cells expressing the protein of

interest. After a suitable period, during which antibodies can be detected in the serum of the animal (usually weeks to months), blood, spleen or other tissues are harvested from the animal. Lymphocytes are isolated from the blood and cultured under specific conditions to generate antibody-forming cells, with antibody being secreted into the culture medium. These cells are detected by any of several means (complement mediated lysis of antigen-bearing cells, fluorescence detection or other) and then isolated using micromanipulation technology. The individual antibody forming cells are then processed for eventual single cell PCR to obtain the expressed Heavy and Light chain genes that encode the specific antibody. Once obtained and sequenced, these genes are cloned into an appropriate expression vector and recombinant, monoclonal antibody produced in a heterologous cell system. These antibodies are then purified via standard methodologies such as the use of protein A affinity columns. These types of methods are further described in Babcook, et al., Proc. Natl. Acad. Sci. (USA) **93:** 7843-7848 (1996); U.S. Patent No. 5,627,052; and PCT WO 92/02551 by Schrader.

Another method involves humanizing a monoclonal antibody by recombinant means to generate antibodies containing human specific and recognizable sequences. See, for review, Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In additional to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the antibody is

obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567); Morrison et al. Proc. Natl. Acad Sci. 81, 6851-6855 (1984).

Methods of making antibody fragments are also known in the art (see for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, (1988), incorporated herein by reference). Antibody fragments of the present invention can be prepared by proteolytic hydrolysis of the antibody or by expression in *E. coli* of DNA encoding the fragment. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment denoted $F(ab')_2$. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5S Fab= monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab' fragments and an Fc fragment directly. These methods are described, for example, in U.S. Patents No. 4,036,945 and No. 4,331,647, and references contained therein. These patents are hereby incorporated in their entireties by reference.

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody. For example, Fv fragments comprise an association of V_H and V_L chains. This

association may be noncovalent or the variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. Preferably, the Fv fragments comprise V_H and V_L chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V_H and V_L domains connected by an oligonucleotide. The structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as *E. coli.* The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing sFvs are described, for example, by Whitlow, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 97 (1991); Bird, et al., Science 242:423-426 (1988); Ladner, et al, US Patent No. 4,946,778; and Pack, et al., Bio/Technology 11:1271-77 (1993).

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 106 (1991).

The invention further contemplates human and humanized forms of non-human (e.g. murine) antibodies. Such humanized antibodies can be chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a nonhuman species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity.

In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the

imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, humanized antibodies can comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the Fv regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see: Jones et al., Nature 321, 522-525 (1986); Reichmann et al., Nature 332, 323-329 (1988); Presta, Curr. Op. Struct. Biol. 2, 593-596 (1992); Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998); U.S. Patent Nos. 4,816,567 and 6,331,415; PCT/GB84/00094; PCT/US86/02269; PCT/US89/00077; PCT/US88/02514; and WO91/09967, each of which is incorporated herein by reference in its entirety.

The invention also provides methods of mutating antibodies to optimize their affinity, selectivity, binding strength or other desirable property. A mutant antibody refers to an amino acid sequence variant of an antibody. In general, one or more of the amino acid residues in the mutant antibody is different from what is present in the reference antibody. Such mutant antibodies necessarily have less than 100% sequence identity or similarity with the reference amino acid sequence. In general, mutant antibodies have at least 75% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody. Preferably, mutant antibodies have at least 80%, more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody.

The antibodies of the invention are isolated antibodies. An isolated antibody is one that has been identified and separated and/or recovered from a component of the environment in which it was produced. Contaminant components of its production environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other

proteinaceous or nonproteinaceous solutes. The term "isolated antibody" also includes antibodies within recombinant cells because at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

If desired, the antibodies of the invention can be purified by any available procedure. For example, the antibodies can be affinity purified by binding an antibody preparation to a solid support to which the antigen used to raise the antibodies is bound. After washing off contaminants, the antibody can be eluted by known procedures. Those of skill in the art will know of various techniques common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (see for example, Coligan, et al., Unit 9, Current Protocols in Immunology, Wiley Interscience, 1991, incorporated by reference).

In preferred embodiments, the antibody will be purified as measurable by at least three different methods: 1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; 2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator; or 3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomasie blue or, preferably, silver stain.

The invention also provides antibodies that can bind to CD83 polypeptides. Sequences of complementarity determining regions (CDRs) or hypervariable regions from light and heavy chains of these anti-CD83 antibodies are provided. For example, a heavy chain variable region having a CDR1 sequence of SYDMT (SEQ ID NO:23), SYDMS (SEQ ID NO:24), DYDLS (SEQ ID NO:25) or SYDMS (SEQ ID NO:26) can be used in an antibody, multimerized antibody or other single- or multi-valent binding moiety to bind to CD83 gene products and/or modulate the immune response. In other embodiments, a heavy chain variable region having a CDR2 sequence of YASGSTYY (SEQ ID NO:27), SSSGTTYY (SEQ ID NO:28), YASGSTYY (SEQ ID NO:29), AIDGNPYY (SEQ ID NO:30) or STAYNSHY (SEQ ID NO:31) can be used in an antibody, multimerized antibody or other single-

or multi-valent binding moiety to bind to CD83 gene products or modulate the immune system. In further embodiments of the invention, a heavy chain variable region having a CDR3 sequence of EHAGYSGDTGH (SEQ ID NO:32), EGAGVSMT (SEQ ID NO:33), EDAGFSNA (SEQ ID NO:34), GAGD (SEQ ID NO:35) or GGSWLD (SEQ ID NO:36) can be used in an antibody, multimerized antibody or other single- or multi-valent binding moiety to bind to CD83 gene products or modulate the immune system.

Moreover, a light chain variable region having a CDR1 sequence of RCAYD (SEQ ID NO:37), RCADVV (SEQ ID NO:38), or RCALV (SEQ ID NO:39) can be used in an antibody, multimerized antibody or other single- or multi-valent binding moiety to bind to CD83 gene products or modulate the immune system. In other embodiments, a light chain variable region having a CDR2 sequence of QSISTY (SEQ ID NO:40), QSVSSY (SEQ ID NO:41), ESISNY (SEQ ID NO:42), KNVYNNNW (SEQ ID NO:43), or QSVYDNDE (SEQ ID NO:98) can be used in an antibody, multimerized antibody or other single- or multi-valent binding moiety to bind to CD83 gene products or modulate the immune system. In further embodiments, a light chain variable region having a CDR3 sequence of QQGYTHSNVDNV (SEQ ID NO:44), QQGYSISDIDNA (SEQ ID NO:45), QCTSGGKFISDGAA (SEQ ID NO:46), AGDYSSSSDNG (SEQ ID NO:47), or QATHYSSDWLTY (SEQ ID NO:48) can be used in an antibody, multimerized antibody or other single- or multi-valent binding moiety to bind to CD83 gene products.

Light and heavy chains that can bind CD83 polypeptides are also provided by the invention. For example, in one embodiment, the invention provides a 20D04 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 light chain is provided below (SEQ ID NO:11).

```
  1 MDMRAPTQLL GLLLLWLPGA RCADVVMTQT PASVSAAVGG
 41 TVTINCQASE SISNYLSWYQ QKPGQPPKLL IYRTSTLASG
 81 VSSRFKGSGS GTEYTLTISG VQCDDVATYY CQCTSGGKFI
121 SDGAAFGGGT EVVVKGDPVA PTVLLFPPSS DEVATGTVTI
161 VCVANKYFPD VTVTWEVDGT TQTTGIENSK TPQNSADCTY
201 NLSSTLTLTS TQYNSHKEYT CKVTQGTTSV VQSFSRKNC
```

A nucleic acid sequence for this 20D04 anti-CD83 light chain is provided below (SEQ ID NO:12).

```
   1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ATGTCGTGAT
  81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
 121 ACAGTCACCA TCAATTGCCA GGCCAGTGAA AGCATTAGCA
 161 ACTACTTATC CTGGTATCAG CAGAAACCAG GGCAGCCTCC
 201 CAAGCTCCTG ATCTACAGGA CATCCACTCT GGCATCTGGG
 241 GTCTCATCGC GGTTCAAAGG CAGTGGATCT GGGACAGAGT
 281 ACACTCTCAC CATCAGCGGC GTGCAGTGTG ACGATGTTGC
 321 CACTTACTAC TGTCAATGCA CTTCTGGTGG GAAGTTCATT
 361 AGTGATGGTG CTGCTTTCGG CGGAGGGACC GAGGTGGTGG
 401 TCAAAGGTGA TCCAGTTGCA CCTACTGTCC TCCTCTTCCC
 441 ACCATCTAGC GATGAGGTGG CAACTGGAAC AGTCACCATC
 481 GTGTGTGTGG CGAATAAATA CTTTCCCGAT GTCACCGTCA
 521 CCTGGGAGGT GGATGGCACC ACCCAAACAA CTGGCATCGA
 561 GAACAGTAAA ACACCGCAGA ATTCTGCAGA TTGTACCTAC
 601 AACCTCAGCA GCACTCTGAC ACTGACCAGC ACACAGTACA
 641 ACAGCCACAA AGAGTACACC TGCAAGGTGA CCCAGGGCAC
 681 GACCTCAGTC GTCCAGAGCT TCAGTAGGAA GAACTGTTAA
```

In another embodiment, the invention provides a 20D04 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 heavy chain is provided below (SEQ ID NO:13).

```
   1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
  41 TVSGFSLSNN AINWVRQAPG KGLEWIGYIW SGGLTYYANW
  81 AEGRFTISKT STTVDLKMTS PTIEDTATYF CARGINNSAL
 121 WGPGTLVTVS SGQPKAPSVF PLAPCCGDTP SSTVTLGCLV
 161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
 201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
 241 LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDVSQDDPEV
 281 QFTWYINNEQ VRTARPPLRE QQFNSTIRVV STLPIAHQDW
 321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
 361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
 401 TPAVLDSDGS YFLYNKLSVP TSEWQRGDVF TCSVMHEALH
 441 NHYTQKSISR SPGK
```

A nucleic acid sequence for this 20D04 anti-CD83 heavy chain is provided below (SEQ ID NO:14).

```
   1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
  41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
  81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACCGTCTCTG GATTCTCCCT CAGTAACAAT GCAATAAACT
 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTAG AGTGGATCGG
 201 ATACATTTGG AGTGGTGGGC TTACATACTA CGCGAACTGG
 241 GCGGAAGGCC GATTCACCAT CTCCAAAACC TCGACTACGG
 281 TGGATCTGAA GATGACCAGT CCGACAATCG AGGACACGGC
 321 CACCTATTTC TGTGCCAGAG GGATTAATAA CTCCGCTTTG
 361 TGGGGCCCAG GCACCCTGGT CACCGTCTCC TCAGGGCAAC
 401 CTAAGGCTCC ATCAGTCTTC CCACTGGCCC CCTGCTGCGG
 441 GGACACACCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
 481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAACT
 521 CGGGCACCCT CACCAATGGG GTACGCACCT TCCCGTCCGT
 561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
 601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
 641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
 681 GCCCTCGACA TGCAGCAAGC CCACGTGCCC ACCCCCTGAA
 721 CTCCTGGGGG GACCGTCTGT CTTCATCTTC CCCCCAAAAC
 761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
 801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCGAGGTG
 841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
 881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
 921 CCGCGTGGTC AGCACCCTCC CCATCGCGCA CCAGGACTGG
 961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
1001 CACTCCCGGC CCCCATCGAG AAAACCATCT CCAAAGCCAG
1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
1081 CCCCGGGAGG AGCTGAGCAG CAGGTCGGTC AGCCTGACCT
```

```
1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA
1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
1201 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
1241 ACAACAAGCT CTCAGTGCCC ACGAGTGAGT GGCAGCGGGG
1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGCAC
1321 AACCACTACA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA
1361 AA
```

In another embodiment, the invention provides a 11G05 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 11G05 light chain is provided below (SEQ ID NO:15).

```
   1 MDTRAPTQLL GLLLLWLPGA RCADVVMTQT PASVSAAVGG
  41 TVTINCQSSK NVYNNNWLSW FQQKPGQPPK LLIYYASTLA
  81 SGVPSRFRGS GSGTQFTLTI SDVQCDDAAT YYCAGDYSSS
 121 SDNGFGGGTE VVVKGDPVAP TVLLFPPSSD EVATGTVTIV
 161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
 201 LSSTLTLTST QYNSHKEYTC KVTQGTTSVV QSFSRKNC
```

A nucleic acid sequence for this 11G05 anti-CD83 light chain is provided below (SEQ ID NO:16).

```
   1 ATGGACACCA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ACGTCGTGAT
  81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
 121 ACAGTCACCA TCAATTGCCA GTCCAGTAAG AATGTTTATA
 161 ATAACAACTG GTTATCCTGG TTTCAGCAGA AACCAGGGCA
 201 GCCTCCCAAG CTCCTGATCT ATTATGCATC CACTCTGGCA
 241 TCTGGGGTCC CATCGCGGTT CAGAGGCAGT GGATCTGGGA
 281 CACAGTTCAC TCTCACCATT AGCGACGTGC AGTGTGACGA
 321 TGCTGCCACT TACTACTGTG CAGGCGATTA TAGTAGTAGT
 361 AGTGATAATG GTTTCGGCGG AGGGACCGAG GTGGTGGTCA
 401 AAGGTGATCC AGTTGCACCT ACTGTCCTCC TCTTCCCACC
 441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
 481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTCACCT
 521 GGGAGGTGGA TGGCACCACC CAAACAACTG GCATCGAGAA
 561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
 601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA
```

```
641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC
681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA
```

In another embodiment, the invention provides a 11G05 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 11G05 heavy chain is provided below (SEQ ID NO:17).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGFTISDY DLSWVRQAPG EGLKYIGFIA IDGNPYYATW
 81 AKGRFTISKT STTVDLKITA PTTEDTATYF CARGAGDLWG
121 PGTLVTVSSG QPKAPSVFPL APCCGDTPSS TVTLGCLVKG
161 YLPEPVTVTW NSGTLTNGVR TFPSVRQSSG LYSLSSVVSV
201 TSSSQPVTCN VAHPATNTKV DKTVAPSTCS KPTCPPPELL
241 GGPSVFIFPP KPKDTLMISR TPEVTCVVVD VSQDDPEVQF
281 TWYINNEQVR TARPPLREQQ FNSTIRVVST LPIAHQDWLR
321 GKEFKCKVHN KALPAPIEKT ISKARGQPLE PKVYTMGPPR
361 EELSSRSVSL TCMINGFYPS DISVEWEKNG KAEDNYKTTP
401 AVLDSDGSYF LYNKLSVPTS EWQRGDVFTC SVMHEALHNH
441 YTQKSISRSP GK
```

A nucleic acid sequence for this 11G05 anti-CD83 heavy chain is provided below (SEQ ID NO:18).

```
  1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGTCTCTG GATTCACCAT CAGTGACTAC GACTTGAGCT
161 GGGTCCGCCA GGCTCCAGGG GAGGGGCTGA AATACATCGG
201 ATTCATTGCT ATTGATGGTA ACCCATACTA CGCGACCTGG
241 GCAAAAGGCC GATTCACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGAA AATCACCGCT CCGACAACCG AAGACACGGC
321 CACGTATTTC TGTGCCAGAG GGGCAGGGGA CCTCTGGGGC
```

```
 361 CCAGGGACCC TCGTCACCGT CTCTTCAGGG CAACCTAAGG
 401 CTCCATCAGT CTTCCCACTG GCCCCCTGCT GCGGGGACAC
 441 ACCCTCTAGC ACGGTGACCT TGGGCTGCCT GGTCAAAGGC
 481 TACCTCCCGG AGCCAGTGAC CGTGACCTGG AACTCGGGCA
 521 CCCTCACCAA TGGGGTACGC ACCTTCCCGT CCGTCCGGCA
 561 GTCCTCAGGC CTCTACTCGC TGAGCAGCGT GGTGAGCGTG
 601 ACCTCAAGCA GCCAGCCCGT CACCTGCAAC GTGGCCCACC
 641 CAGCCACCAA CACCAAAGTG GACAAGACCG TTGCGCCCTC
 681 GACATGCAGC AAGCCCACGT GCCCACCCCC TGAACTCCTG
 721 GGGGGACCGT CTGTCTTCAT CTTCCCCCCA AAACCCAAGG
 761 ACACCCTCAT GATCTCACGC ACCCCCGAGG TCACATGCGT
 801 GGTGGTGGAC GTGAGCCAGG ATGACCCCGA GGTGCAGTTC
 841 ACATGGTACA TAAACAACGA GCAGGTGCGC ACCGCCCGGC
 881 CGCCGCTACG GGAGCAGCAG TTCAACAGCA CGATCCGCGT
 921 GGTCAGCACC CTCCCCATCG CGCACCAGGA CTGGCTGAGG
 961 GGCAAGGAGT TCAAGTGCAA AGTCCACAAC AAGGCACTCC
1001 CGGCCCCCAT CGAGAAAACC ATCTCCAAAG CCAGAGGGCA
1041 GCCCCTGGAG CCGAAGGTCT ACACCATGGG CCCTCCCCGG
1081 GAGGAGCTGA GCAGCAGGTC GGTCAGCCTG ACCTGCATGA
1120 TCAACGGCTT CTACCCTTCC GACATCTCGG TGGAGTGGGA
1161 GAAGAACGGG AAGGCAGAGG ACAACTACAA GACCACGCCG
1201 GCCGTGCTGG ACAGCGACGG CTCCTACTTC CTCTACAACA
1241 AGCTCTCAGT GCCCACGAGT GAGTGGCAGC GGGGCGACGT
1281 CTTCACCTGC TCCGTGATGC ACGAGGCCTT GCACAACCAC
1321 TACACGCAGA AGTCCATCTC CCGCTCTCCG GGTAAA
```

In another embodiment, the invention provides a 14C12 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 14C12 light chain is provided below (SEQ ID NO:19).

```
   1 MDXRAPTQLL GLLLLWLPGA RCALVMTQTP ASVSAAVGGT
  41 VTINCQSSQS VYDNDELSWY QQKPGQPPKL LIYLASKLAS
  81 GVPSRFKGSG SGTQFALTIS GVQCDDAATY YCQATHYSSD
```

```
121 WYLTFGGGTE VVVKGDPVAP TVLLFPPSSD EVATGTVTIV
161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
201 LSSTLTLTST QYNSHKEYTC KVTQGTTSVV QSFSRKNC
```

A nucleic acid sequence for this 14C12 anti-CD83 light chain is provided below (SEQ ID NO:20).

```
  1 ATGGACATRA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCC TTGTGATGAC
 81 CCAGACTCCA GCCTCCGTGT CTGCAGCTGT GGGAGGCACA
121 GTCACCATCA ATTGCCAGTC CAGTCAGAGT GTTTATGATA
161 ACGACGAATT ATCCTGGTAT CAGCAGAAAC CAGGGCAGCC
201 TCCCAAGCTC CTGATCTATC TGGCATCCAA GTTGGCATCT
241 GGGGTCCCAT CCCGATTCAA AGGCAGTGGA TCTGGGACAC
281 AGTTCGCTCT CACCATCAGC GGCGTGCAGT GTGACGATGC
321 TGCCACTTAC TACTGTCAAG CCACTCATTA TAGTAGTGAT
361 TGGTATCTTA CTTTCGGCGG AGGGACCGAG GTGGTGGTCA
401 AAGGTGATCC AGTTGCACCT ACTGTCCTCC TCTTCCCACC
441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTCACCT
521 GGGAGGTGGA TGGCACCACC CAAACAACTG GCATCGAGAA
561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA
641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC
681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA
```

In another embodiment, the invention provides a 14C12 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 14C12 heavy chain is provided below (SEQ ID NO:21).

```
  1 METGLRWLLL VAVLKGVHCQ SVEESGGRLV TPGTPLTLTC
 41 TASGFSRSSY DMSWVRQAPG KGLEWVGVIS TAYNSHYASW
 81 AKGRFTISRT STTVDLKMTS LTTEDTATYF CARGGSWLDL
121 WGQGTLVTVS SGQPKAPSVF PLAPCCGDTP SSTVTLGCLV
161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
241 LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDVSQDDPEV
281 QFTWYINNEQ VRTARPPLRE QQFNSTIRVV STLPIAHQDW
321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
```

361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT

401 TPAVLDSDGS YFLYNKLSVP TSEWQRGDVF TCSVMHEALH

441 NHYTQKSISR SPGK

A nucleic acid sequence for this 14C12 anti-CD83 heavy chain is provided below (SEQ ID NO:22).

```
  1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCACTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGCCTCTG GATTCTCCCG CAGCAGCTAC GACATGAGCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGGTCGG
201 AGTCATTAGT ACTGCTTATA ACTCACACTA CGCGAGCTGG
241 GCAAAAGGCC GATTCACCAT CTCCAGAACC TCGACCACGG
281 TGGATCTGAA AATGACCAGT CTGACAACCG AAGACACGGC
321 CACCTATTTC TGTGCCAGAG GGGGTAGTTG GTTGGATCTC
361 TGGGGCCAGG GCACCCTGGT CACCGTCTCC TCAGGGCAAC
401 CTAAGGCTCC ATCAGTCTTC CCACTGGCCC CCTGCTGCGG
441 GGACACACCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAACT
521 CGGGCACCCT CACCAATGGG GTACGCACCT TCCCGTCCGT
561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
681 GCCCTCGACA TGCAGCAAGC CCACGTGCCC ACCCCCTGAA
721 CTCCTGGGGG GACCGTCTGT CTTCATCTTC CCCCCAAAAC
761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCGAGGTG
841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
921 CCGCGTGGTC AGCACCCTCC CCATCGCGCA CCAGGACTGG
961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
```

```
1001 CACTCCCGGC CCCCATCGAG AAAACCATCT CCAAAGCCAG
1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
1081 CCCCGGGAGG AGCTGAGCAG CAGGTCGGTC AGCCTGACCT
1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA
1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
1200 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
1241 ACAACAAGCT CTCAGTGCCC ACGAGTGAGT GGCAGCGGGG
1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGCAC
1321 AACCACTACA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA
1361 AA
```

In another embodiment, the invention provides a M83 020B08L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08L light chain is provided below (SEQ ID NO:58).

```
   1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
  41 VTIKCQASQS ISTYLDWYQQ KPGQPPKLLI YDASDLASGV
  81 PSRFKGSGSG TQFTLTISDL ECADAATYYC QQGYTHSNVD
 121 NVFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
 161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
 201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC
```

A nucleic acid sequence for this M83 020B08L anti-CD83 light chain is provided below (SEQ ID NO:59).

```
   1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
  81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
 121 GTCACCATCA AGTGCCAGGC CAGTCAGAGC ATTAGTACCT
 161 ACTTAGACTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
 201 GCTCCTGATC TATGATGCAT CCGATCTGGC ATCTGGGGTC
 241 CCATCGCGGT TCAAAGGCAG TGGATCTGGG ACACAGTTCA
 281 CTCTCACCAT CAGCGACCTG GAGTGTGCCG ATGCTGCCAC
 321 TTACTACTGT CAACAGGGTT ATACACATAG TAATGTTGAT
 361 AATGTTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
 401 ATCCAGTTGC ACCTACTGTC CTCCTCTTCC CACCATCTAG
```

```
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
481 GCGAATAAAT ACTTTCCCGA TGTCACCGTC ACCTGGGAGG
521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A
```

In another embodiment, the invention provides a M83 020B08H heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08H heavy chain is provided below (SEQ ID NO:60).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGFSLSSY DMTWVRQAPG KGLEWIGIIY ASGTTYYANW
 81 AKGRFTISKT STTVDLKVTS PTIGDTATYF CAREGAGVSM
121 TLWGPGTLVT VSSGQPKAPS VFPLAPCCGD TPSSTVTLGC
161 LVKGYLPEPV TVTWNSGTLT NGVRTFPSVR QSSGLYSLSS
201 VVSVTSSSQP VTCNVAHPAT NTKVDKTVAP STCSKPTCPP
241 PELLGGPSVF IFPPKPKDTL MISRTPEVTC VVVDVSQDDP
281 EVQFTWYINN EQVRTARPPL REQQFNSTIR VVSTLPIAHQ
321 DWLRGKEFKC KVHNKALPAP IEKTISKARG QPLEPKVYTM
361 GPPREELSSR SVSLTCMING FYPSDISVEW EKNGKAEDNY
401 KTTPAVLDSD GSYFLYNKLS VPTSEWQRGD VFTCSVMHEA
441 LHNHYTQKSI SRSPGK
```

A nucleic acid sequence for this M83 020B08H anti-CD83 heavy chain is provided below (SEQ ID NO:61).

```
  1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGTCTCTG GATTCTCCCT CAGCAGCTAC GACATGACCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGATCGG
201 AATCATTTAT GCTAGTGGTA CCACATACTA CGCGAACTGG
241 GCGAAAGGCC GATTCACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGAA AGTCACCAGT CCGACAATCG GGGACACGGC
321 CACCTATTTC TGTGCCAGAG AGGGGGCTGG TGTTAGTATG
361 ACCTTGTGGG GCCCAGGCAC CCTGGTCACC GTCTCCTCAG
401 GGCAACCTAA GGCTCCATCA GTCTTCCCAC TGGCCCCCTG
441 CTGCGGGGAC ACACCCTCTA GCACGGTGAC CTTGGGCTGC
481 CTGGTCAAAG GCTACCTCCC GGAGCCAGTG ACCGTGACCT
521 GGAACTCGGG CACCCTCACC AATGGGGTAC GCACCTTCCC
561 GTCCGTCCGG CAGTCCTCAG GCCTCTACTC GCTGAGCAGC
601 GTGGTGAGCG TGACCTCAAG CAGCCAGCCC GTCACCTGCA
641 ACGTGGCCCA CCCAGCCACC AACACCAAAG TGGACAAGAC
681 CGTTGCGCCC TCGACATGCA GCAAGCCCAC GTGCCCACCC
```

```
 721 CCTGAACTCC TGGGGGGACC GTCTGTCTTC ATCTTCCCCC
 761 CAAAACCCAA GGACACCCTC ATGATCTCAC GCACCCCCGA
 801 GGTCACATGC GTGGTGGTGG ACGTGAGCCA GGATGACCCC
 841 GAGGTGCAGT TCACATGGTA CATAAACAAC GAGCAGGTGC
 881 GCACCGCCCG GCCGCCGCTA CGGGAGCAGC AGTTCAACAG
 921 CACGATCCGC GTGGTCAGCA CCCTCCCCAT CGCGCACCAG
 961 GACTGGCTGA GGGGCAAGGA GTTCAAGTGC AAAGTCCACA
1001 ACAAGGCACT CCCGGCCCCC ATCGAGAAAA CCATCTCCAA
1041 AGCCAGAGGG CAGCCCCTGG AGCCGAAGGT CTACACCATG
1081 GGCCCTCCCC GGGAGGAGCT GAGCAGCAGG TCGGTCAGCC
1121 TGACCTGCAT GATCAACGGC TTCTACCCTT CCGACATCTC
1161 GGTGGAGTGG GAGAAGAACG GGAAGGCAGA GGACAACTAC
1201 AAGACCACGC CGGCCGTGCT GGACAGCGAC GGCTCCTACT
1241 TCCTCTACAA CAAGCTCTCA GTGCCCACGA GTGAGTGGCA
1281 GCGGGGCGAC GTCTTCACCT GCTCCGTGAT GCACGAGGCC
1321 TTGCACAACC ACTACACGCA GAAGTCCATC TCCCGCTCTC
1361 CGGGTAAA
```

In another embodiment, the invention provides a M83 006G05L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L light chain is provided below (SEQ ID NO:62).

```
   1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
  41 VAIKCQASQS VSSYLAWYQQ KPGQPPKPLI YEASMLAAGV
  81 SSRFKGSGSG TDFTLTISDL ECDDAATYYC QQGYSISDID
 121 NAFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
 161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
 201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC
```

A nucleic acid sequence for M83 006G05L anti-CD83 light chain is provided below (SEQ ID NO:63).

```
   1 ATGGACATGA GGGCCCCCAC TCAACTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
  81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
 121 GTCGCCATCA AGTGCCAGGC CAGTCAGAGC GTTAGTAGTT
 161 ACTTAGCCTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
 201 GCCCCTGATC TACGAAGCAT CCATGCTGGC GGCTGGGGTC
 241 TCATCGCGGT TCAAAGGCAG TGGATCTGGG ACAGACTTCA
 281 CTCTCACCAT CAGCGACCTG GAGTGTGACG ATGCTGCCAC
 321 TTACTATTGT CAACAGGGTT ATTCTATCAG TGATATTGAT
 361 AATGCTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
```

```
401 ATCCAGTTGC ACCTACTGTC CTCCTCTTCC CACCATCTAG
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
481 GCGAATAAAT ACTTTCCCGA TGTCACCGTC ACCTGGGAGG
521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A
```

In another embodiment, the invention provides a M83 006G05L heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L heavy chain is provided below (SEQ ID NO:64).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV SPGTPLTLTC
 41 TASGFSLSSY DMSWVRQAPG KGLEYIGIIS SSGSTYYASW
 81 AKGRFTISKT STTVDLEVTS LTTEDTATYF CSREHAGYSG
121 DTGHLWGPGT LVTVSSGQPK APSVFPLAPC CGDTPSSTVT
161 LGCLVKGYLP EPVTVTWNSG TLTNGVRTFP SVRQSSGLYS
201 LSSVVSVTSS SQPVTCNVAH PATNTKVDKT VAPSTCSKPT
241 CPPPELLGGP SVFIFPPKPK DTLMISRTPE VTCVVVDVSQ
281 DDPEVQFTWY INNEQVRTAR PPLREQQFNS TIRVVSTLPI
321 AHQDWLRGKE FKCKVHNKAL PAPIEKTISK ARGQPLEPKV
361 YTMGPPREEL SSRSVSLTCM INGFYPSDIS VEWEKNGKAE
401 DNYKTTPAVL DSDGSYFLYN KLSVPTSEWQ RGDVFTCSVM
441 HEALHNHYTQ KSISRSPGK
```

A nucleic acid sequence for this M83 006G05L anti-CD83 heavy chain is provided below (SEQ ID NO:65).

```
  1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC TCGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGCCTCTG GATTCTCCCT CAGTAGCTAC GACATGAGCT
161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATACATCGG
201 AATCATTAGT AGTAGTGGTA GCACATACTA CGCGAGCTGG
241 GCGAAAGGCC GATTCACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGGA AGTGACCAGT CTGACAACCG AGGACACGGC
321 CACCTATTTC TGTAGTAGAG AACATGCTGG TTATAGTGGT
361 GATACGGGTC ACTTGTGGGG CCCAGGCACC CTGGTCACCG
401 TCTCCTCGGG GCAACCTAAG GCTCCATCAG TCTTCCCACT
441 GGCCCCCTGC TGCGGGGACA CACCCTCTAG CACGGTGACC
481 TTGGGCTGCC TGGTCAAAGG CTACCTCCCG GAGCCAGTGA
521 CCGTGACCTG GAACTCGGGC ACCCTCACCA ATGGGGTACG
561 CACCTTCCCG TCCGTCCGGC AGTCCTCAGG CCTCTACTCG
601 CTGAGCAGCG TGGTGAGCGT GACCTCAAGC AGCCAGCCCG
```

```
 641 TCACCTGCAA CGTGGCCCAC CCAGCCACCA ACACCAAAGT
 681 GGACAAGACC GTTGCGCCCT CGACATGCAG CAAGCCCACG
 721 TGCCCACCCC CTGAACTCCT GGGGGGACCG TCTGTCTTCA
 761 TCTTCCCCCC AAAACCCAAG GACACCCTCA TGATCTCACG
 801 CACCCCCGAG GTCACATGCG TGGTGGTGGA CGTGAGCCAG
 841 GATGACCCCG AGGTGCAGTT CACATGGTAC ATAAACAACG
 881 AGCAGGTGCG CACCGCCCGG CCGCCGCTAC GGGAGCAGCA
 921 GTTCAACAGC ACGATCCGCG TGGTCAGCAC CCTCCCCATC
 961 GCGCACCAGG ACTGGCTGAG GGGCAAGGAG TTCAAGTGCA
1001 AAGTCCACAA CAAGGCACTC CCGGCCCCCA TCGAGAAAAC
1041 CATCTCCAAA GCCAGAGGGC AGCCCCTGGA GCCGAAGGTC
1081 TACACCATGG GCCCTCCCCG GGAGGAGCTG AGCAGCAGGT
1121 CGGTCAGCCT GACCTGCATG ATCAACGGCT TCTACCCTTC
1162 CGACATCTCG GTGGAGTGGG AGAAGAACGG GAAGGCAGAG
1201 GACAACTACA AGACCACGCC GGCCGTGCTG GACAGCGACG
1241 GCTCCTACTT CCTCTACAAC AAGCTCTCAG TGCCCACGAG
1281 TGAGTGGCAG CGGGGCGACG TCTTCACCTG CTCCGTGATG
1321 CACGAGGCCT TGCACAACCA CTACACGCAG AAGTCCATCT
1361 CCCGCTCTCC GGGTAAA
```

In another embodiment, the invention provides a 96G08 light chain that can bind to CD83 polypeptides and can inhibit proliferation of human peripheral blood mononuclear cells (PBMCs). The amino acid sequence for this 96G08 light chain is provided below (SEQ ID NO:70).

```
  1 MDTRAPTQLL GLLLLWLPGA TFAQVLTQTA SPVSAPVGGT
 41 VTINCQSSQS VYNNDFLSWY QQKPGQPPKL LIYYASTLAS
 81 GVPSRFKGSG SGTQFTLTIS DLECDDAATY YCTGTYGNSA
121 WYEDAFGGGT EVVVKRTPVA PTVLLFPPSS AELATGTATI
161 VCVANKYFPD GTVTWKVDGI TQSSGINNSR TPQNSADCTY
201 NLSSTLTLSS DEYNSHDEYT CQVAQDSGSP VVQSFSRKSC
```

The amino acid sequence for this 96G08 light chain with the CDR regions identified by underlining is provided below (SEQ ID NO:70).

```
  1 MDTRAPTQLL GLLLLWLPGA TFAQVLTQTA SPVSAPVGGT
 41 VTINCQSSQS VYNNDFLSWY QQKPGQPPKL LIYYASTLAS
 81 GVPSRFKGSG SGTQFTLTIS DLECDDAATY YCTGTYGNSA
121 WYEDAFGGGT EVVVKRTPVA PTVLLFPPSS AELATGTATI
161 VCVANKYFPD GTVTWKVDGI TQSSGINNSR TPQNSADCTY
201 NLSSTLTLSS DEYNSHDEYT CQVAQDSGSP VVQSFSRKSC
```

Hence, the CDR regions in the 96G08 light chain include amino acid sequences QSSQSVYNNDFLS (SEQ ID NO:71), YASTLAS (SEQ ID NO:72), and TGTYGNSAWYEDA (SEQ ID NO:73).

A nucleic acid sequence for this 96G08 anti-CD83 light chain is provided below (SEQ ID NO:74).

```
   1 ATGGACACGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC ACATTTGCGC AAGTGCTGAC
  81 CCAGACTGCA TCGCCCGTGT CTGCACCTGT GGGAGGCACA
 121 GTCACCATCA ATTGCCAGTC CAGTCAGAGT GTTTATAATA
 161 ACGACTTCTT ATCCTGGTAT CAGCAGAAAC CAGGGCAGCC
 201 TCCCAAACTC CTGATCTATT ATGCATCCAC TCTGGCATCT
 241 GGGGTCCCAT CCCGGTTCAA AGGCAGTGGA TCTGGGACAC
 281 AGTTCACTCT CACCATCAGC GACCTGGAGT GTGACGATGC
 321 TGCCACTTAC TACTGTACAG GCACTTATGG TAATAGTGCT
 361 TGGTACGAGG ATGCTTTCGG CGGAGGGACC GAGGTGGTGG
 401 TCAAACGTAC GCCAGTTGCA CCTACTGTCC TCCTCTTCCC
 441 ACCATCTAGC GCTGAGCTGG CAACTGGAAC AGCCACCATC
 481 GTGTGCGTGG CGAATAAATA CTTTCCCGAT GGCACCGTCA
 521 CCTGGAAGGT GGATGGCATC ACCCAAAGCA GCGGCATCAA
 561 TAACAGTAGA ACACCGCAGA ATTCTGCAGA TTGTACCTAC
 601 AACCTCAGCA GTACTCTGAC ACTGAGCAGC GACGAGTACA
 641 ACAGCCACGA CGAGTACACC TGCCAGGTGG CCCAGGACTC
 681 AGGCTCACCG GTCGTCCAGA GCTTCAGTAG GAAGAGCTGT
 721 TAG
```

This nucleic acid sequence for the 96G08 anti-CD83 light chain with CDR regions identified by underlining is provided below (SEQ ID NO:99).

```
   1 ATGGACACGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC ACATTTGCGC AAGTGCTGAC
  81 CCAGACTGCA TCGCCCGTGT CTGCACCTGT GGGAGGCACA
 121 GTCACCATCA ATTGCCAGTC CAGTCAGAGT GTTTATAATA
 161 ACGACTTCTT ATCCTGGTAT CAGCAGAAAC CAGGGCAGCC
```

201 TCCCAAACTC CTGATCTATT ATGCATCCAC TCTGGCATCT

241 GGGGTCCCAT CCCGGTTCAA AGGCAGTGGA TCTGGGACAC

281 AGTTCACTCT CACCATCAGC GACCTGGAGT GTGACGATGC

321 GCCACTTACT ACTGTACAGG CACTTATGGT AATAGTGCTT

361 GGTACGAGGA TGCTTTCGGC GGAGGGACCG AGGTGGTGGT

401 CAAACGTACG CCAGTTGCAC CTACTGTCCT CCTCTTCCCA

441 CCATCTAGCG CTGAGCTGGC AACTGGAACA GCCACCATCG

481 TGTGCGTGGC GAATAAATAC TTTCCCGATG GCACCGTCAC

521 CTGGAAGGTG GATGGCATCA CCCAAAGCAG CGGCATCAAT

561 AACAGTAGAA CACCGCAGAA TTCTGCAGAT TGTACCTACA

601 ACCTCAGCAG TACTCTGACA CTGAGCAGCG ACGAGTACAA

641 CAGCCACGAC GAGTACACCT GCCAGGTGGC CCAGGACTCA

681 GGCTCACCGG TCGTCCAGAG CTTCAGTAGG AAGAGCTGTT

Hence, the CDR regions in the 96G08 light chain include nucleic acid sequences CAGTCCAGTCAGAGTGTTTATAATA (SEQ ID NO:75), ATGCATCCACTCTGGCATCT (SEQ ID NO:76), and ACAGGCACTTATGGT AATAGTGCTT (SEQ ID NO:77).

In another embodiment, the invention provides a 96G08 heavy chain that can bind to CD83 polypeptides and can inhibit proliferation of human peripheral blood mononuclear cells (PBMCs). The amino acid sequence for this 96G08 heavy chain is provided below (SEQ ID NO:78).

1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC

41 TVSGIDLSSD GISWVRQAPG KGLEWIGIIS SGGNTYYASW

81 AKGRFTISRT STTVDLKMTS LTTEDTATYF CARVVGGTYS

121 IWGQGTLVTV SSASTKGPSV YPLAPGSAAQ TNSMVTLGCL

161 VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ SDLYTLSSSV

201 TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI

241 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP

281 EVQFSWFVDD VEVHTAQTQP REEQFNSTFR SVSELPIMHQ

321 DWLNGKEFKC RVNSAAFPAP IEKTISKTKG RPKAPQVYTI

361 PPPKEQMAKD KVSLTCMITD FFPEDITVEW QWNGQPAENY

401 KNTQPIMDTD GSYFVYSKLN VQKSNWEAGN TFTCSVLHEG

441 LHNHHTEKSL SHSPGK

The amino acid sequence for the 96G08 heavy chain with the CDR regions identified by underlining is provided below (SEQ ID NO:78).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGIDLSSD GISWVRQAPG KGLEWIGIIS SGGNTYYASW
 81 AKGRFTISRT STTVDLKMTS LTTEDTATYF CARVVGGTYS
121 IWGQGTLVTV SSASTKGPSV YPLAPGSAAQ TNSMVTLGCL
161 VKGYFPEPVT VTWNSGSLSS GVHTFPAVLQ SDLYTLSSSV
201 TVPSSTWPSE TVTCNVAHPA SSTKVDKKIV PRDCGCKPCI
241 CTVPEVSSVF IFPPKPKDVL TITLTPKVTC VVVDISKDDP
281 EVQFSWFVDD VEVHTAQTQP REEQFNSTFR SVSELPIMHQ
321 DWLNGKEFKC RVNSAAFPAP IEKTISKTKG RPKAPQVYTI
361 PPPKEQMAKD KVSLTCMITD FFPEDITVEW QWNGQPAENY
401 KNTQPIMDTD GSYFVYSKLN VQKSNWEAGN TFTCSVLHEG
441 LHNHHTEKSL SHSPGK
```

Hence, the CDR regions in the 96G08 heavy chain include amino acid sequences SDGIS (SEQ ID NO:79), IISSGGNTYYASWAKG (SEQ ID NO:80) and VVGGTYSI (SEQ ID NO:81).

A nucleic acid sequence for the 96G08 anti-CD83 heavy chain is provided below (SEQ ID NO:82).

```
   1 ATGGAGACTG GGCTGCGCTG GCTTCTCCTG GTCGCTGTGC
  41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
  81 TCGCCTGGTC ACACCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACAGTGTCTG GAATCGACCT CAGTAGCGAT GGAATAAGCT
 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGATCGG
 201 AATCATTAGT AGTGGTGGTA ACACATACTA CGCGAGCTGG
 241 GCAAAAGGCC GATTCACCAT CTCCAGAACC TCGACCACGG
 281 TGGATCTGAA GATGACCAGT CTGACAACCG AGGACACGGC
 321 CACCTATTTC TGTGCCAGAG TTGTTGGTGG TACTTATAGC
 361 ATCTGGGGCC AGGGCACCCT CGTCACCGTC TCGAGCGCTT
 401 CTACAAAGGG CCCATCTGTC TATCCACTGG CCCCTGGATC
 441 TGCTGCCCAA ACTAACTCCA TGGTGACCCT GGGATGCCTG
 481 GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 521 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC
 561 TGTCCTGCAG TCTGACCTCT ACACTCTGAG CAGCTCAGTG
 601 ACTGTCCCCT CCAGCACCTG GCCCAGCGAG ACCGTCACCT
 641 GCAACGTTGC CCACCCGGCC AGCAGCACCA AGGTGGACAA
 681 GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 721 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC
 761 CAAAGCCCAA GGATGTGCTC ACCATTACTC TGACTCCTAA
 801 GGTCACGTGT GTTGTGGTAG ACATCAGCAA GGATGATCCC
```

```
 841 GAGGTCCAGT TCAGCTGGTT TGTAGATGAT GTGGAGGTGC
 881 ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 921 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG
 961 GACTGGCTCA ATGGCAAGGA GTTCAAATGC AGGGTCAACA
1001 GTGCAGCTTT CCCTGCCCCC ATCGAGAAAA CCATCTCCAA
1041 AACCAAAGGC AGACCGAAGG CTCCACAGGT GTACACCATT
1081 CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
1121 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC
1161 TGTGGAGTGG CAGTGGAATG GGCAGCCAGC GGAGAACTAC
1201 AAGAACACTC AGCCCATCAT GGACACAGAT GGCTCTTACT
1241 TCGTCTACAG CAAGCTCAAT GTGCAGAAGA GCAACTGGGA
1281 GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1321 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC
1361 CTGGTAAATG A
```

The nucleic acid sequence for the 96G08 anti-CD83 heavy chain with CDR regions identified by underlining is provided below is provided below (SEQ ID NO:82).

```
   1 ATGGAGACTG GGCTGCGCTG GCTTCTCCTG GTCGCTGTGC
  41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
  81 TCGCCTGGTC ACACCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACAGTGTCTG GAATCGACCT CAGTAGCGAT GGAATAAGCT
 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGATCGG
 201 AATCATTAGT AGTGGTGGTA ACACATACTA CGCGAGCTGG
 241 GCAAAAGGCC GATTCACCAT CTCCAGAACC TCGACCACGG
 281 TGGATCTGAA GATGACCAGT CTGACAACCG AGGACACGGC
 321 CACCTATTTC TGTGCCAGAG TTGTTGGTGG TACTTATAGC
 361 ATCTGGGGCC AGGGCACCCT CGTCACCGTC TCGAGCGCTT
 401 CTACAAAGGG CCCATCTGTC TATCCACTGG CCCCTGGATC
 441 TGCTGCCCAA ACTAACTCCA TGGTGACCCT GGGATGCCTG
 481 GTCAAGGGCT ATTTCCCTGA GCCAGTGACA GTGACCTGGA
 521 ACTCTGGATC CCTGTCCAGC GGTGTGCACA CCTTCCCAGC
 561 TGTCCTGCAG TCTGACCTCT ACACTCTGAG CAGCTCAGTG
 601 ACTGTCCCCT CCAGCACCTG GCCCAGCGAG ACCGTCACCT
 641 GCAACGTTGC CCACCCGGCC AGCAGCACCA AGGTGGACAA
 681 GAAAATTGTG CCCAGGGATT GTGGTTGTAA GCCTTGCATA
 721 TGTACAGTCC CAGAAGTATC ATCTGTCTTC ATCTTCCCCC
 761 CAAAGCCCAA GGATGTGCTC ACCATTACTC TGACTCCTAA
 801 GGTCACGTGT GTTGTGGTAG ACATCAGCAA GGATGATCCC
 841 GAGGTCCAGT TCAGCTGGTT TGTAGATGAT GTGGAGGTGC
 881 ACACAGCTCA GACGCAACCC CGGGAGGAGC AGTTCAACAG
 921 CACTTTCCGC TCAGTCAGTG AACTTCCCAT CATGCACCAG
 961 GACTGGCTCA ATGGCAAGGA GTTCAAATGC AGGGTCAACA
1001 GTGCAGCTTT CCCTGCCCCC ATCGAGAAAA CCATCTCCAA
1041 AACCAAAGGC AGACCGAAGG CTCCACAGGT GTACACCATT
1081 CCACCTCCCA AGGAGCAGAT GGCCAAGGAT AAAGTCAGTC
```

```
1121 TGACCTGCAT GATAACAGAC TTCTTCCCTG AAGACATTAC
1161 TGTGGAGTGG CAGTGGAATG GGCAGCCAGC GGAGAACTAC
1201 AAGAACACTC AGCCCATCAT GGACACAGAT GGCTCTTACT
1241 TCGTCTACAG CAAGCTCAAT GTGCAGAAGA GCAACTGGGA
1281 GGCAGGAAAT ACTTTCACCT GCTCTGTGTT ACATGAGGGC
1321 CTGCACAACC ACCATACTGA GAAGAGCCTC TCCCACTCTC
1361 CTGGTAAATG A
```

Hence, the CDR regions in the 96G08 anti-CD83 heavy chain include AGCGATGGAATAAGC (SEQ ID NO:83), ATCATTAGTAGTGGTGGTA ACACATACTACGCGAGCTGGGCAAAAGGC (SEQ ID NO:84), and G TTGTTGGTGG TACTTATAGC ATC (SEQ ID NO:85).

In another embodiment, the invention provides a 95F04 light chain that can bind to CD83 polypeptides and can inhibit proliferation of human peripheral blood mononuclear cells (PBMCs). The amino acid sequence for this 95F04 light chain is provided below (SEQ ID NO:86).

```
  1 MDTRAPTQLL GLLLLWLPGA TFAQAVVTQT TSPVSAPVGG
 41 TVTINCQSSQ SVYGNNELSW YQQKPGQPPK LLIYQASSLA
 81 SGVPSRFKGS GSGTQFTLTI SDLECDDAAT YYCLGEYSIS
121 ADNHFGGGTE VVVKRTPVAP TVLLFPPSSA ELATGTATIV
161 CVANKYFPDG TVTWKVDGIT QSSGINNSRT PQNSADCTYN
201 LSSTLTLSSD EYNSHDEYTC QVAQDSGSPV VQSFSRKSC
```

The amino acid sequence for the 95F04 anti-CD83 light chain with the CDR regions identified by underlining is provided below (SEQ ID NO:86).

```
  1 MDTRAPTQLL GLLLLWLPGA TFAQAVVTQT TSPVSAPVGG
 41 TVTINCQSSQ SVYGNNELSW YQQKPGQPPK LLIYQASSLA
 81 SGVPSRFKGS GSGTQFTLTI SDLECDDAAT YYCLGEYSIS
121 ADNHFGGGTE VVVKRTPVAP TVLLFPPSSA ELATGTATIV
161 CVANKYFPDG TVTWKVDGIT QSSGINNSRT PQNSADCTYN
201 LSSTLTLSSD EYNSHDEYTC QVAQDSGSPV VQSFSRKSC
```

Hence, the CDR regions in the 95F04 anti-CD83 light chain include amino acid sequences QSSQSVYGNNELS (SEQ ID NO:87), QASSLAS (SEQ ID NO:88) and LGEYSISADNH (SEQ ID NO:89).

A nucleic acid sequence for this 95F04 anti-CD83 light chain is provided below (SEQ ID NO:90).

```
1 ATGGACACGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
```

```
  41 TGCTCTGGCT CCCAGGTGCC ACATTTGCCC AAGCCGTGGT
  81 GACCCAGACT ACATCGCCCG TGTCTGCACC TGTGGGAGGC
 121 ACAGTCACCA TCAATTGCCA GTCCAGTCAG AGTGTTTATG
 161 GTAACAACGA ATTATCCTGG TATCAGCAGA AACCAGGGCA
 201 GCCTCCCAAG CTCCTGATCT ACCAGGCATC CAGCCTGGCA
 241 TCTGGGGTCC CATCGCGGTT CAAAGGCAGT GGATCTGGGA
 281 CACAGTTCAC TCTCACCATC AGCGACCTGG AGTGTGACGA
 321 TGCTGCCACT TACTACTGTC TAGGCGAATA TAGCATTAGT
 361 GCTGATAATC ATTTCGGCGG AGGGACCGAG GTGGTGGTCA
 401 AACGTACGCC AGTTGCACCT ACTGTCCTCC TCTTCCCACC
 441 ATCTAGCGCT GAGCTGGCAA CTGGAACAGC CACCATCGTG
 481 TGCGTGGCGA ATAAATACTT TCCCGATGGC ACCGTCACCT
 521 GGAAGGTGGA TGGCATCACC CAAAGCAGCG GCATCAATAA
 561 CAGTAGAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
 601 CTCAGCAGTA CTCTGACACT GAGCAGCGAC GAGTACAACA
 641 GCCACGACGA GTACACCTGC CAGGTGGCCC AGGACTCAGG
 681 CTCACCGGTC GTCCAGAGCT TCAGTAGGAA GAGCTGTTAG
```

The nucleic acid sequence for the 95F04 anti-CD83 light chain with CDR regions identified by underlining is provided below (SEQ ID NO:90).

```
   1 ATGGACACGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
  41 TGCTCTGGCT CCCAGGTGCC ACATTTGCCC AAGCCGTGGT
  81 GACCCAGACT ACATCGCCCG TGTCTGCACC TGTGGGAGGC
 121 ACAGTCACCA TCAATTGCCA GTCCAGTCAG AGTGTTTATG
 161 GTAACAACGA ATTATCCTGG TATCAGCAGA AACCAGGGCA
 201 GCCTCCCAAG CTCCTGATCT ACCAGGCATC CAGCCTGGCA
 241 TCTGGGGTCC CATCGCGGTT CAAAGGCAGT GGATCTGGGA
 281 CACAGTTCAC TCTCACCATC AGCGACCTGG AGTGTGACGA
 321 TGCTGCCACT TACTACTGTC TAGGCGAATA TAGCATTAGT
 361 GCTGATAATC ATTTCGGCGG AGGGACCGAG GTGGTGGTCA
 401 AACGTACGCC AGTTGCACCT ACTGTCCTCC TCTTCCCACC
 441 ATCTAGCGCT GAGCTGGCAA CTGGAACAGC CACCATCGTG
 481 TGCGTGGCGA ATAAATACTT TCCCGATGGC ACCGTCACCT
 521 GGAAGGTGGA TGGCATCACC CAAAGCAGCG GCATCAATAA
 561 CAGTAGAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
 601 CTCAGCAGTA CTCTGACACT GAGCAGCGAC GAGTACAACA
 641 GCCACGACGA GTACACCTGC CAGGTGGCCC AGGACTCAGG
 681 CTCACCGGTC GTCCAGAGCT TCAGTAGGAA GAGCTGTTAG
```

In another embodiment, the invention provides a 95F04 heavy chain that can bind to CD83 polypeptides and can inhibit proliferation of human peripheral blood mononuclear cells (PBMCs). The amino acid sequence for this 95F04 heavy chain is provided below (SEQ ID NO:91).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGIDLSSN AMIWVRQAPR EGLEWIGAMD SNSRTYYATW
 81 AKGRFTISRT SSITVDLKIT SPTTEDTATY FCARGDGGSS
121 DYTEMWGPGT LVTVSSASTK GPSVYPLAPG SAAQTNSMVT
161 LGCLVKGYFP EPVTVTWNSG SLSSGVHTFP AVLQSDLYTL
201 SSSVTVPSST WPSETVTCNV AHPASSTKVD KKIVPRDCGC
241 KPCICTVPEV SSVFIFPPKP KDVLTITLTP KVTCVVVDIS
281 KDDPEVQFSW FVDDVEVHTA QTQPREEQFN STFRSVSELP
321 IMHQDWLNGK EFKCRVNSAA FPAPIEKTIS KTKGRPKAPQ
361 VYTIPPPKEQ MAKDKVSLTC MITDFFPEDI TVEWQWNGQP
401 AENYKNTQPI MDTDGSYFVY SKLNVQKSNW EAGNTFTCSV
441 LHEGLHNHHT EKSLSHSPGK
```

The amino acid sequence for the 95F04 anti-CD83 heavy chain with the CDR regions identified by underlining is provided below (SEQ ID NO:91).

```
  1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
 41 TVSGIDLSSN AMIWVRQAPR EGLEWIGAMD SNSRTYYATW
 81 AKGRFTISRT SSITVDLKIT SPTTEDTATY FCARGDGGSS
121 DYTEMWGPGT LVTVSSASTK GPSVYPLAPG SAAQTNSMVT
161 LGCLVKGYFP EPVTVTWNSG SLSSGVHTFP AVLQSDLYTL
201 SSSVTVPSST WPSETVTCNV AHPASSTKVD KKIVPRDCGC
241 KPCICTVPEV SSVFIFPPKP KDVLTITLTP KVTCVVVDIS
281 KDDPEVQFSW FVDDVEVHTA QTQPREEQFN STFRSVSELP
321 IMHQDWLNGK EFKCRVNSAA FPAPIEKTIS KTKGRPKAPQ
361 VYTIPPPKEQ MAKDKVSLTC MITDFFPEDI TVEWQWNGQP
401 AENYKNTQPI MDTDGSYFVY SKLNVQKSNW EAGNTFTCSV
441 LHEGLHNHHT EKSLSHSPGK
```

Hence, the CDR regions in the 95F04 anti-CD83 heavy chain include amino acid sequences SNAMI (SEQ ID NO:92), AMDSNSRTYYATWAKG (SEQ ID NO:93), and GDGGSSDYTEM (SEQ ID NO:94).

A nucleic acid sequence for this 95F04 anti-CD83 heavy chain is provided below (SEQ ID NO:95).

```
   1 ATGGAGACTG GGCTGCGCTG GCTTCTCCTG GTCGCTGTGC
  41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
  81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACAGTCTCTG GAATCGACCT CAGTAGCAAT GCAATGATCT
 161 GGGTCCGCCA GGCTCCAAGG GAGGGGCTGG AATGGATCGG
 201 AGCCATGGAT AGTAATAGTA GGACGTACTA CGCGACCTGG
 241 GCGAAAGGCC GATTCACCAT CTCCAGAACC TCGTCGATTA
 281 CGGTGGATCT GAAAATCACC AGTCCGACAA CCGAGGACAC
 321 GGCCACCTAT TTCTGTGCCA GAGGGGATGG TGGCAGTAGT
 361 GATTATACAG AGATGTGGGG CCCAGGGACC CTCGTCACCG
 401 TCTCGAGCGC TTCTACAAAG GGCCCATCTG TCTATCCACT
 441 GGCCCCTGGA TCTGCTGCCC AAACTAACTC CATGGTGACC
 481 CTGGGATGCC TGGTCAAGGG CTATTTCCCT GAGCCAGTGA
 521 CAGTGACCTG GAACTCTGGA TCCCTGTCCA GCGGTGTGCA
 561 CACCTTCCCA GCTGTCCTGC AGTCTGACCT CTACACTCTG
 601 AGCAGCTCAG TGACTGTCCC CTCCAGCACC TGGCCCAGCG
 641 AGACCGTCAC CTGCAACGTT GCCCACCCGG CCAGCAGCAC
 681 CAAGGTGGAC AAGAAAATTG TGCCCAGGGA TTGTGGTTGT
 721 AAGCCTTGCA TATGTACAGT CCCAGAAGTA TCATCTGTCT
 761 TCATCTTCCC CCCAAAGCCC AAGGATGTGC TCACCATTAC
 801 TCTGACTCCT AAGGTCACGT GTGTTGTGGT AGACATCAGC
 841 AAGGATGATC CCGAGGTCCA GTTCAGCTGG TTTGTAGATG
 881 ATGTGGAGGT GCACACAGCT CAGACGCAAC CCCGGGAGGA
 921 GCAGTTCAAC AGCACTTTCC GCTCAGTCAG TGAACTTCCC
 961 ATCATGCACC AGGACTGGCT CAATGGCAAG GAGTTCAAAT
1001 GCAGGGTCAA CAGTGCAGCT TTCCCTGCCC CCATCGAGAA
1041 AACCATCTCC AAAACCAAAG GCAGACCGAA GGCTCCACAG
1081 GTGTACACCA TTCCACCTCC CAAGGAGCAG ATGGCCAAGG
1141 ATAAAGTCAG TCTGACCTGC ATGATAACAG ACTTCTTCCC
1161 TGAAGACATT ACTGTGGAGT GGCAGTGGAA TGGGCAGCCA
1201 GCGGAGAACT ACAAGAACAC TCAGCCCATC ATGGACACAG
1241 ATGGCTCTTA CTTCGTCTAC AGCAAGCTCA ATGTGCAGAA
1281 GAGCAACTGG GAGGCAGGAA ATACTTTCAC CTGCTCTGTG
1321 TTACATGAGG GCCTGCACAA CCACCATACT GAGAAGAGCC
1361 TCTCCCACTC TCCTGGTAAA TGA
```

A related nucleic acid sequence for the 95F04 anti-CD83 light chain is provided below (SEQ ID NO:96).

```
   1 ATGGAGACTG GGCTGCGCTG GCTTCTCCTG GTCGCTGTGC
  41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
  81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACAGTCTCTG GAATCGACCT CAGTAGCAAT GCAATGATCT
 161 GGGTCCGCCA GGCTCCAAGG GAGGGGCTGG AATGGATCGG
 201 AGCCATGGAT AGTAATAGTA GGACGTACTA CGCGACCTGG
 241 GCGAAAGGCC GATTCACCAT CTCCAGAACC TCGTCGATTA
 281 CGGTGGATCT GAAAATCACC AGTCCGACAA CCGAGGACAC
```

```
 321 GGCCACCTAT TTCTGTGCCA GAGGGGATGG TGGCAGTAGT
 361 GATTATACAG AGATGTGGGG CCCAGGGACC CTCGTCACCG
 401 TCTCGAGCGC TTCTACAAAG GGCCCATCTG TCTATCCACT
 441 GGCCCCTGGA TCTGCTGCCC AAACTAACTC CATGGTGACC
 481 CTGGGATGCC TGGTCAAGGG CTATTTCCCT GAGCCAGTGA
 521 CAGTGACCTG GAACTCTGGA TCCCTGTCCA GCGGTGTGCA
 561 CACCTTCCCA GCTGTCCTGC AGTCTGACCT CTACACTCTG
 601 AGCAGCTCAG TGACTGTCCC CTCCAGCACC TGGCCCAGCG
 641 AGACCGTCAC CTGCAACGTT GCCCACCCGG CCAGCAGCAC
 681 CAAGGTGGAC AAGAAAATTG TGCCCAGGGA TTGTGGTTGT
 721 AAGCCTTGCA TATGTACAGT CCCAGAAGTA TCATCTGTCT
 761 TCATCTTCCC CCCAAAGCCC AAGGATGTGC TCACCATTAC
 801 TCTGACTCCT AAGGTCACGT GTGTTGTGGT AGACATCAGC
 841 AAGGATGATC CCGAGGTCCA GTTCAGCTGG TTTGTAGATG
 881 ATGTGGAGGT GCACACAGCT CAGACGCAAC CCCGGGAGGA
 921 GCAGTTCAAC AGCACTTTCC GCTCAGTCAG TGAACTTCCC
 961 ATCATGCACC AGGACTGGCT CAATGGCAAG GAGTTCAAAT
1001 GCAGGGTCAA CAGTGCAGCT TTCCCTGCCC CCATCGAGAA
1041 AACCATCTCC AAAACCAAAG GCAGACCGAA GGCTCCACAG
1081 GTGTACACCA TTCCACCTCC CAAGGAGCAG ATGGCCAAGG
1121 ATAAAGTCAG TCTGACCTGC ATGATAACAG ACTTCTTCCC
1161 TGAAGACATT ACTGTGGAGT GGCAGTGGAA TGGGCAGCCA
1201 GCGGAGAACT ACAAGAACAC TCAGCCCATC ATGGACACAG
1241 ATGGCTCTTA CTTCGTCTAC AGCAAGCTCA ATGTGCAGAA
1281 GAGCAACTGG GAGGCAGGAA ATACTTTCAC CTGCTCTGTG
1321 TTACATGAGG GCCTGCACAA CCACCATACT GAGAAGAGCC
1361 TCTCCCACTC TCCTGGTAAA TGA
```

CD83 Modulation of the Immune System

The invention also provides compositions and methods for decreasing inappropriate immune responses in animals, including humans. According to the invention, the CD83 gene has a profound effect upon T cell activity. In particular, CD4+ T cells require CD83-related functions. Without CD83, CD4+ T cell activation and/or proliferation is impaired. The therapeutic manipulation of CD83 may thus represent a mechanism for the specific regulation of T cell function in the treatment of T cell mediated diseases, including autoimmune disorders. For example, antibodies capable of blocking CD83 function can be used as therapeutics in the treatment of immune diseases.

In some embodiments, the CD83-related compositions and methods of the invention can be used in the treatment of autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against

"self tissues" and that promote the production of cytokines and auto-antibodies involved in the pathology of the diseases. Modulation of T cell activity by modulating CD83 can have an effect on the course of the autoimmune disease.

Non-limiting examples of autoimmune diseases and disorders having an autoimmune component that may be treated according to the invention include diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), multiple sclerosis, myasthenia gravis, systemic lupus erythematosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis.

As illustrated and provided herein, anti-CD83 antibodies can inhibit T cell proliferation. The efficacy of anti-CD83-related compositions for treating autoimmune diseases can be tested in the animal models provided herein or other models of human diseases (e.g., EAE as a model of multiple sclerosis and the NOD mice as a model for diabetes). Such animal models include the mrl/lpr/lpr mouse as a model for lupus erythematosus, murine collagen-induced arthritis as a model for rheumatoid arthritis, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856). A CD83-modulatory (e.g., inhibitory) agent of the invention is administered to test animals and the course of the disease in the test animals is then monitored by the standard methods for the particular model being used. Effectiveness of the modulatory agent

is evidenced by amelioration of the disease condition in animals treated with the agent as compared to untreated animals (or animals treated with a control agent).

Similarly, the compositions and methods of the invention that involve decreasing CD83 function can be used to decrease transplant rejection and prolong survival of the tissue graft. These methods can be used both in solid organ transplantation and in bone marrow transplantation (e.g., to inhibit graft-versus-host disease). These methods can involve either direct administration of a CD83 inhibitory agent to the transplant recipient or ex vivo treatment of cells obtained from the subject (e.g., T cells, Th1 cells, B cells, non-lymphoid cells) with an inhibitory agent followed by re-administration of the cells to the subject.

According to the invention, any agent that can modulate CD83 or to further decrease T cell levels can also be used in the compositions and methods of the invention. In some embodiments, anti-CD83 antibodies of the invention are used to either activate or inhibit CD83 activity.

Stimulating or Inhibiting CD83

According to the invention, any agent that can inhibit CD83 from performing its natural functions can be used in the compositions and methods of the invention as a CD83 inhibitory agent. Indicators that CD83 activity is inhibited include decreased T cell counts, increased IL-4 cytokine levels, increased IL-10 levels, decreased IL-2 production, and decreased TNF levels relative to uninhibited levels in wild type CD83 cells.

Examples of CD83 inhibitors include anti-CD83 antibodies, CD83 anti-sense nucleic acids (e.g. nucleic acids that can hybridize to CD83 nucleic acids), organic compounds, peptides and agents that can mutate an endogenous CD83 gene.

In some embodiments, the CD83 stimulatory or inhibitory agents are proteins, for example, CD83 gene products, anti-CD83 antibody preparations, CD83 inhibitors, peptides and protein factors that can promote CD83 transcription or translation. In other embodiments, the CD83 stimulatory or inhibitory agents are peptides or organic molecules. Such proteins, organic molecules and organic

molecules can be prepared and/or purified as described herein or by methods available in the art, and administered as provided herein.

In other embodiments, the CD83 inhibitory agents can be nucleic acids including recombinant expression vectors or expression cassettes encoding CD83 anti-sense nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors. Such nucleic acids can be operably linked to a promoter that is functional in a mammalian cell, and then introduced into cells of the subject mammal using methods known in the art for introducing nucleic acid (e.g., DNA) into cells.

The "promoter functional in a mammalian cell" or "mammalian promoter" is capable of directing transcription of a polypeptide coding sequence operably linked to the promoter. The promoter should generally be active in T cells and antigen presenting cells and may be obtained from a gene that is expressed in T cells or antigen presenting cells. However, it need not be a T cell-specific or an antigen presenting cell specific-promoter. Instead, the promoter may be selected from any mammalian or viral promoter that can function in a T cell. Hence the promoter may be an actin promoter, an immunoglobulin promoter, a heat-shock promoter, or a viral promoter obtained from the genome of viruses such as adenoviruses, retroviruses, lentiviruses, herpes viruses, including but not limited to, polyoma virus, fowlpox virus, adenovirus 2, bovine papilloma virus, avian sarcoma virus, cytomegalovirus (CMV), hepatitis-B virus, Simian Virus 40 (SV40), Epstein Barr virus (EBV), feline immunodeficiency virus (FIV), and Sra, or are respiratory synsitial viral promoters (RSV) or long terminal repeats (LTRs) of a retrovirus, i.e., a Moloney Murine Leukemia Virus (MoMuLv) (Cepko et al. (1984) Cell 37:1053-1062). The promoter functional in a mammalian cell can be inducible or constitutive.

Any cloning procedure used by one of skill in the art can be employed to make the expression vectors or expression that comprise a promoter operably linked to a CD83 nucleic acid, CD83 transcription factor or a nucleic acid encoding an anti-CD83 antibody. *See, e.g.,* Sambrook et al., Molecular Cloning, A Laboratory

Manual, Cold Spring Harbor Laboratory, N.Y., 1989; Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 2001.

After constructing an expression vector or an expression cassette encoding CD83 transcription factors, CD83 anti-sense nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors, mammalian cells can be transformed with the vector or cassette. Examples of such methods include:

Direct Injection: Naked DNA can be introduced into cells in vivo by directly injecting the DNA into the cells (see e.g., Acsadi et al. (1991) Nature 332:815-818; Wolff et al. (1990) Science 247:1465-1468). For example, a delivery apparatus (e.g., a "gene gun") for injecting DNA into cells in vivo can be used. Such an apparatus is commercially available (e.g., from BioRad).

Receptor-Mediated DNA Uptake: Naked DNA can also be introduced into cells in vivo by complexing the DNA to a cation, such as polylysine, which is coupled to a ligand for a cell-surface receptor (see for example Wu, G. and Wu, C. H. (1988) J. Biol. Chem. 263:14621; Wilson et al. (1992) J. Biol. Chem. 267:963-967; and U.S. Pat. No. 5,166,320). Binding of the DNA-ligand complex to the receptor facilitates uptake of the DNA by receptor-mediated endocytosis. A DNA-ligand complex linked to adenovirus capsids that naturally disrupt endosomes, thereby releasing material into the cytoplasm can be used to avoid degradation of the complex by intracellular lysosomes (see for example Curiel et al. (1991) Proc. Natl. Acad Sci. USA 88:8850; Cristiano et al. (1993) Proc. Natl. Acad. Sci. USA 90:2122-2126).

Retroviruses: Defective retroviruses are well characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A. D. (1990) Blood 76:271). A recombinant retrovirus can be constructed having nucleotide sequences of interest incorporated into the retroviral genome. Additionally, portions of the retroviral genome can be removed to render the retrovirus replication defective. The replication defective retrovirus is then packaged into virions that can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells in vitro or in vivo with such viruses can be found in Current Protocols in Molecular Biology,

Ausubel, F. M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals. Examples of suitable retroviruses include pLJ, pZIP, pWE and pEM which are available to those skilled in the art. Examples of suitable packaging virus lines include ? Crip, ? Cre, ? 2 and ? Am. Retroviruses have been used to introduce a variety of genes into many different cell types, including epithelial cells, endothelial cells, lymphocytes, myoblasts, hepatocytes, bone marrow cells, in vitro and/or in vivo (see for example Eglitis, et al. (1 985) Science 230:1395-1398; Danos and Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:6460-6464; Wilson et al. (1 988) Proc. Natl. Acad. Sci. USA 85:3014-3018; Armentano et al. (1990) Proc. Natl. Acad. Sci. USA 87:6141-6145; Huber et al. (1991) Proc. Natl. Acad. Sci. USA 88:8039-8043; Ferry et al. (1991) Proc. Natl. Acad. Sci. USA 88:8377-8381; Chowdhury et al. (1991) Science 254:1802-1805; van Beusechem et al. (1992) Proc. Natl. Acad. Sci. USA 89:7640-7644; Kay et al. (1992) Human Gene Therapy 3:641-647; Dai et al. (1992) Proc. Natl. Acad. Sci USA 89:10892-10895; Hwu et al. (1993) J. Immunol. 150:4104-4115; U.S. Pat. Nos. 4,868,116; 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573). Retroviral vectors require target cell division in order for the retroviral genome (and foreign nucleic acid inserted into it) to be integrated into the host genome to stably introduce nucleic acid into the cell. Thus, it may be necessary to stimulate replication of the target cell.

Adenoviruses: The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner et al. (1988) BioTechniques 6:616; Rosenfeld et al. (1991) Science 252:431-434; and Rosenfeld et al. (1992) Cell 68:143-155. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are available to those skilled in the art. Recombinant adenoviruses are advantageous in that they do not require dividing cells to be effective gene delivery vehicles and can be used to infect a wide variety of cell types, including airway epithelium (Rosenfeld et al. (1992) cited supra), endothelial cells

(Lemarchand et al. (1992) Proc. Natl. Acad. Sci. USA 89:6482-6486), hepatocytes (Herz and Gerard (1993) Proc. Natl. Acad Sci. USA 90:2812-2816) and muscle cells (Quantin et al. (1992) Proc. Natl. Acad. Sci. USA 89:2581-2584). Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (e.g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner et al. cited supra; Haj-Ahmand and Graham (1986) J. Virol. 57:267). Most replication-defective adenoviral vectors currently in use are deleted for all or parts of the viral E1 and E3 genes but retain as much as 80% of the adenoviral genetic material.

Adeno-Associated Viruses: Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al. Curr. Topics in Micro. and Immunol. (1992) 158:97-129). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte et al. (1992) Am. J. Respir. Cell. Mol. Biol. 7:349-356; Samulski et al. (1989) J. Virol. 63:3822-3828; and McLaughlin et al. (1989) J. Virol. 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al. (1985) Mol. Cell. Biol. 5:3251-3260 can be used to introduce DNA into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors (see for example Hermonat et al. (1984) Proc. Natl. Acad. Sci. USA 81:6466-6470; Tratschin et al. (1985) Mol. Cell. Biol. 4:2072-2081; Wondisford et al. (1988) Mol. Endocrinol. 2:32-39; Tratschin et al. (1984) J Virol. 51:611-619; and Flotte et al. (1993) J. Biol. Chem. 268:3781-3790).

Transformed mammalian cells can then be identified and administered to the mammal from whence they came to permit expression of a CD83 transcription factor, CD83 anti-sense nucleic acid, intracellular antibody capable of binding to

CD83 proteins, or dominant negative CD83 inhibitors. The efficacy of a particular expression vector system and method of introducing nucleic acid into a cell can be assessed by standard approaches routinely used in the art. For example, DNA introduced into a cell can be detected by a filter hybridization technique (e.g., Southern blotting). RNA produced by transcription of an introduced DNA can be detected, for example, by Northern blotting, RNase protection or reverse transcriptase-polymerase chain reaction (RT-PCR). The CD83 gene product can be detected by an appropriate assay, for example, by immunological detection of a produced CD83 protein, such as with a CD83-specific antibody.

Anti-sense Nucleic Acids

Anti-sense nucleic acids can be used to inhibit the function of CD83. In general, the function of CD83 RNA is inhibited, for example, by administering to a mammal a nucleic acid that can inhibit the functioning of CD83 RNA. Nucleic acids that can inhibit the function of a CD83 RNA can be generated from coding and non-coding regions of the CD83 gene. However, nucleic acids that can inhibit the function of a CD83 RNA are often selected to be complementary to CD83 nucleic acids that are naturally expressed in the mammalian cell to be treated with the methods of the invention. In some embodiments, the nucleic acids that can inhibit CD83 RNA functions are complementary to CD83 sequences found near the 5' end of the CD83 coding region. For example, nucleic acids that can inhibit the function of a CD83 RNA can be complementary to the 5' region of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10.

A nucleic acid that can inhibit the functioning of a CD83 RNA need not be 100% complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Instead, some variability the sequence of the nucleic acid that can inhibit the functioning of a CD83 RNA is permitted. For example, a nucleic acid that can inhibit the functioning of a CD83 RNA from a human can be complementary to a nucleic acid encoding either a human or a mouse CD83 gene product.

Moreover, nucleic acids that can hybridize under moderately or highly stringent hybridization conditions to a nucleic acid comprising SEQ ID NO:1, SEQ

ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 are sufficiently complementary to inhibit the functioning of a CD83 RNA and can be utilized in the methods of the invention.

"Stringent hybridization conditions" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization are somewhat sequence dependent, and may differ depending upon the environmental conditions of the nucleic acid. For example, longer sequences tend to hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Laboratory Techniques in Biochemistry and Molecular biology-Hybridization with Nucleic Acid Probes, page 1, chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays" Elsevier, New York (1993). See also, J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y., pp 9.31-9.58 (1989); J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y. (3rd ed. 2001).

Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific double-stranded sequence at a defined ionic strength and pH. For example, under "highly stringent conditions" or "highly stringent hybridization conditions" a nucleic acid will hybridize to its complement to a detectably greater degree than to other sequences (e.g., at least 2- fold over background). By controlling the stringency of the hybridization and/or washing conditions nucleic acids that are 100% complementary can be hybridized.

For DNA-DNA hybrids, the T_m can be approximated from the equation of Meinkoth and Wahl Anal. Biochem. 138:267-284 (1984):

T_m 81.5°C + 16.6 (log M) +0.41 (%GC) - 0.61 (% form) - 500/L

where M is the molarity of monovalent cations, %GC is the percentage of guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The T_m is the temperature (under defined ionic strength and pH) at which 50% of a complementary target sequence hybridizes to a perfectly matched probe.

Very stringent conditions are selected to be equal to the T_m for a particular probe.

Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity can hybridize. Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.

Exemplary low stringency conditions include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl and 0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1.0 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 60°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at 37°C, and a wash in 0. 1X SSC at 60 to 65°C.

The degree of complementarity or sequence identity of hybrids obtained during hybridization is typically a function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. The type and length of hybridizing nucleic acids also affects whether hybridization will occur and whether any hybrids formed will be stable under a given set of hybridization and wash conditions.

An example of stringent hybridization conditions for hybridization of complementary nucleic acids that have more than 100 complementary residues on a filter in a Southern or Northern blot is 50% formamide with 1 mg of heparin at 42°C, with the hybridization being carried out overnight. An example of highly stringent conditions is 0.1 5 M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (see also, Sambrook, infra). Often, a high stringency wash is preceded by a low stringency wash to remove background probe signal. An example of medium stringency for a duplex of, e.g., more than 100 nucleotides, is 1x SSC at 45°C for 15 minutes. An

example low stringency wash for a duplex of, e.g., more than 100 nucleotides, is 4-6x SSC at 40°C for 15 minutes. For short probes (e.g., about 10 to 50 nucleotides), stringent conditions typically involve salt concentrations of less than about 1.0M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3, and the temperature is typically at least about 30°C.

Stringent conditions can also be achieved with the addition of destabilizing agents such as formamide. In general, a signal to noise ratio of 2x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization. Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the proteins that they encode are substantially identical. This occurs, e.g., when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code.

The following are examples of sets of hybridization/wash conditions that may be used to detect and isolate homologous nucleic acids that are substantially identical to reference nucleic acids of the present invention: a reference nucleotide sequence preferably hybridizes to the reference nucleotide sequence in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 2X SSC, 0.1% SDS at 50°C, more desirably in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 1X SSC, 0.1% SDS at 50°C, more desirably still in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 0.5X SSC, 0.1% SDS at 50°C, preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 50°C, more preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 65°C.

In general, T_m is reduced by about 1°C for each 1% of mismatching. Thus, T_m, hybridization, and/or wash conditions can be adjusted to hybridize to sequences of the desired sequence identity. For example, if sequences with >90% identity are sought, the T_m can be decreased 10°C. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4°C lower than the

thermal melting point (T_m); moderately stringent conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10°C lower than the thermal melting point (T_m); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20°C lower than the thermal melting point (T_m).

If the desired degree of mismatching results in a T_m of less than 45°C (aqueous solution) or 32°C (formamide solution), it is preferred to increase the SSC concentration so that a higher temperature can be used. An extensive guide to the hybridization of nucleic acids is found in Tijssen (1993) Laboratory Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Acid Probes, Part 1, Chapter 2 (Elsevier, New York); and Ausubel et al., eds. (1995) Current Protocols in Molecular Biology, Chapter 2 (Greene Publishing and Wiley - Interscience, New York). See Sambrook et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Plainview, New York). Using these references and the teachings herein on the relationship between T_m, mismatch, and hybridization and wash conditions, those of ordinary skill can generate variants of the present homocysteine S-methyltransferase nucleic acids.

Precise complementarity is therefore not required for successful duplex formation between a nucleic acid that can inhibit a CD83 RNA and the complementary coding sequence of a CD83 RNA. Inhibitory nucleic acid molecules that comprise, for example, 2, 3, 4, or 5 or more stretches of contiguous nucleotides that are precisely complementary to a CD83 coding sequence, each separated by a stretch of contiguous nucleotides that are not complementary to adjacent CD83 coding sequences, can inhibit the function of CD83 RNA. In general, each stretch of contiguous nucleotides is at least 4, 5, 6, 7, or 8 or more nucleotides in length. Non-complementary intervening sequences are preferably 1, 2, 3, or 4 nucleotides in length. One skilled in the art can easily use the calculated melting point of an anti-sense nucleic acid hybridized to a sense nucleic acid to determine the degree of mismatching that will be tolerated between a particular anti-sense nucleic acid and a particular CD83 RNA.

Nucleic acids that complementary a CD83 RNA can be administered to a mammal or to directly to the site of the inappropriate immune system activity.

Alternatively, nucleic acids that are complementary to a CD83 RNA can be generated by transcription from an expression cassette that has been administered to a mammal. For example, a complementary RNA can be transcribed from a CD83 nucleic acid that has been inserted into an expression cassette in the 3' to 5' orientation, that is, opposite to the usual orientation employed to generate sense RNA transcripts. Hence, to generate a complementary RNA that can inhibit the function of an endogenous CD83 RNA, the promoter would be positioned to transcribe from a 3' site towards the 5' end of the CD83 coding region.

In some embodiments an RNA that can inhibit the function of an endogenous CD83 RNA is an anti-sense oligonucleotide. The anti-sense oligonucleotide is complementary to at least a portion of the coding sequence of a gene comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Such anti-sense oligonucleotides are generally at least six nucleotides in length, but can be about 8, 12, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides long. Longer oligonucleotides can also be used. CD83 anti-sense oligonucleotides can be provided in a DNA construct and introduced into cells whose division is to be decreased, for example, into CD4+ T cells, Th-1 cells, Th-2 cells or lymphocyte precursor cells.

Anti-sense oligonucleotides can be composed of deoxyribonucleotides, ribonucleotides, or a combination of both. Oligonucleotides can be synthesized endogenously from transgenic expression cassettes or vectors as described herein. Alternatively, such oligonucleotides can be synthesized manually or by an automated synthesizer, by covalently linking the 5' end of one nucleotide with the 3' end of another nucleotide with non-phosphodiester internucleotide linkages such alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, alkylphosphonates, phosphoramidates, phosphate esters, carbamates, acetamidate, carboxymethyl esters, carbonates, and phosphate triesters. See Brown, 1994, Meth. Mol. Biol. 20:1-8; Sonveaux, 1994, Meth. Mol. Biol. 26:1-72; Uhlmann et al., 1990, Chem. Rev. 90:543-583.

CD83 anti-sense oligonucleotides can be modified without affecting their ability to hybridize to a CD83 RNA. These modifications can be internal or at one

or both ends of the anti-sense molecule. For example, internucleoside phosphate linkages can be modified by adding peptidyl, cholesteryl or diamine moieties with varying numbers of carbon residues between these moieties and the terminal ribose. Modified bases and/or sugars, such as arabinose instead of ribose, or a 3', 5'-substituted oligonucleotide in which the 3' hydroxyl group or the 5' phosphate group are substituted, can also be employed in a modified anti-sense oligonucleotide. These modified oligonucleotides can be prepared by methods available in the art. Agrawal et al., 1992, Trends Biotechnol. 10:152-158; Uhlmann et al., 1990, Chem. Rev. 90:543-584; Uhlmann et al., 1987, Tetrahedron. Lett. 215:3539-3542.

In one embodiment of the invention, expression of a CD83 gene is decreased using a ribozyme. A ribozyme is an RNA molecule with catalytic activity. See, e.g., Cech, 1987, Science 236: 1532-1539; Cech, 1990, Ann. Rev. Biochem. 59:543-568; Cech, 1992, Curr. Opin. Struct. Biol. 2: 605-609; Couture and Stinchcomb, 1996, Trends Genet. 12: 510-515. Ribozymes can be used to inhibit gene function by cleaving an RNA sequence, as is known in the art (see, e.g., Haseloff et al., U.S. Pat. No. 5,641,673).

CD83 nucleic acids complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 can be used to generate ribozymes that will specifically bind to mRNA transcribed from a CD83 gene. Methods of designing and constructing ribozymes that can cleave other RNA molecules in trans in a highly sequence specific manner have been developed and described in the art (see Haseloff et al. (1988), Nature 334:585-591). For example, the cleavage activity of ribozymes can be targeted to specific RNAs by engineering a discrete "hybridization" region into the ribozyme. The hybridization region contains a sequence complementary to the target RNA and thus specifically hybridizes with the target (see, for example, Gerlach et al., EP 321,201). The target sequence can be a segment of about 10, 12, 15, 20, or 50 contiguous nucleotides selected from a nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Longer complementary sequences can be used to increase the affinity of the hybridization sequence for the target. The hybridizing and cleavage regions of the ribozyme can be integrally related; thus, upon hybridizing to the target RNA

through the complementary regions, the catalytic region of the ribozyme can cleave the target.

Other CD83 Modulating Molecules

A wide variety of molecules may be used to modulate CD83 activity or function. Such molecules can also be used to modulate the immune system independent of CD83. Compositions and methods for modulating CD83 activity or expression can include these molecules as well as other components. Representative examples that are discussed in more detail below include transcription factors, RNA-binding factors, organic molecules, or peptides.

RNA-Binding Factors:

One class of molecules that can be used to modulate the CD83 gene is the RNA binding factors. Such factors include those described in PCT/EP01/14820 and other sources.

For example, the HuR protein (Genbank accession number U38175) has the ability to specifically bind to CD83 RNA at AU-rich elements or sites. Such AU-rich elements comprise sequences such as AUUUA (SEQ ID NO:49), AUUUUA (SEQ ID NO:50) and AUUUUUA (SEQ ID NO:51). Binding by such HuR proteins to CD83 mRNA is thought to increase the stability, transport and translation of CD83 mRNA, and thereby increase the expression of CD83 polypeptides. Hence, CD83 expression may be increase by administering HuR proteins or nucleic acids to a mammal.

Conversely, CD83 expression may be decreased by administering factors that block HuR binding to CD83 mRNA. Factors that block HuR binding include proteins or nucleic acids that can bind to the AU-rich elements normally bound by HuR, for example, nucleic acids or anti-sense nucleic acids that are complementary to AU-rich elements.

Organic Molecules:

Numerous organic molecules may be used to modulate the immune system.

These compounds include any compound that can interact with a component of the immune system. Such compounds may interact directly with CD83, indirectly with CD83 or with some other polypeptide, cell or factor that plays a role in the function of the immune system. In some embodiments, the organic molecule can bind to a CD83 polypeptide or a CD83 nucleic acid.

Organic molecules can be tested or assayed for their ability to modulate CD83 activity, CD83 function or for their ability to modulate components of the immune system. For example, within one embodiment of the invention suitable organic molecules may be selected either from a chemical library, wherein chemicals are assayed individually, or from combinatorial chemical libraries where multiple compounds are assayed at once, then deconvoluted to determine and isolate the most active compounds.

Representative examples of such combinatorial chemical libraries include those described by Agrafiotis et al., "System and method of automatically generating chemical compounds with desired properties," U.S. Patent No. 5,463,564; Armstrong, R.W., "Synthesis of combinatorial arrays of organic compounds through the use of multiple component combinatorial array syntheses," WO 95/02566; Baldwin, J.J. et al., "Sulfonamide derivatives and their use," WO 95/24186; Baldwin, J.J. et al., "Combinatorial dihydrobenzopyran library," WO 95/30642; Brenner, S., "New kit for preparing combinatorial libraries," WO 95/16918; Chenera, B. et al., "Preparation of library of resin-bound aromatic carbocyclic compounds," WO 95/16712; Ellman, J.A., "Solid phase and combinatorial synthesis of benzodiazepine compounds on a solid support," U.S. Patent No. 5,288,514; Felder, E. et al., "Novel combinatorial compound libraries," WO 95/16209; Lerner, R. et al., "Encoded combinatorial chemical libraries," WO 93/20242; Pavia, M.R. et al., "A method for preparing and selecting pharmaceutically useful non-peptide compounds from a structurally diverse universal library," WO 95/04277; Summerton, J.E. and D.D. Weller, "Morpholino-subunit combinatorial library and method," U.S. Patent No. 5,506,337; Holmes, C., "Methods for the Solid Phase Synthesis of Thiazolidinones, Metathiazanones, and Derivatives thereof," WO 96/00148; Phillips, G.B. and G.P. Wei, "Solid-phase

Synthesis of Benzimidazoles," *Tet. Letters 37*:4887-90, 1996; Ruhland, B. et al., "Solid-supported Combinatorial Synthesis of Structurally Diverse -Lactams," *J. Amer. Chem. Soc. 111*:253-4, 1996; Look, G.C. et al., "The Indentification of Cyclooxygenase-1 Inhibitors from 4-Thiazolidinone Combinatorial Libraries," *Bioorg and Med. Chem. Letters 6*:707-12, 1996.

Peptides:

Peptide molecules that modulate the immune system may be obtained through the screening of combinatorial peptide libraries. Such libraries may either be prepared by one of skill in the art (*see e.g.*, U.S. Patent Nos. 4,528,266 and 4,359,535, and Patent Cooperation Treaty Publication Nos. WO 92/15679, WO 92/15677, WO 90/07862, WO 90/02809, or purchased from commercially available sources (*e.g.*, New England Biolabs Ph.D.™ Phage Display Peptide Library Kit).

Methods of Using the CD83 Mutant Mouse

In one embodiment, the invention provides a method for identifying ligands, receptors, therapeutic drugs and other molecules that can modulate the phenotype of the mutant CD83 in vivo. This method involves administering a test compound to the mutant CD83 mouse of the invention and observing whether the compound causes a change in the phenotype of the mutant mouse. Changes in phenotype that are of interest include increases or decreases in T cells (especially CD4+ T cells), increases or decreases in GMCSF, IL-2, IL-4 or IL-10 cytokine production, increases or decreases in inflammation, increases or decreases in dendritic cell function and other T cell responses known to one of skill in the art.

Test compounds can be screened in vitro to ascertain whether they interact directly with CD83. In vitro screening can, for example, identify whether a test compound or molecule can bind to the cytoplasmic tail or the membrane-associated portions of CD83. Such information, combined with observation of the in vivo phenotype before and after administration of the test compound provides further

insight into the function of CD83 and provides targets for manipulation T cell activation and other functions modulated by CD83.

The invention is not limited to identification of molecules that directly associate with CD83. The in vivo screening methods provided herein can, also identify test compounds that have an indirect effect on CD83, or that partially or completely replace a function of CD83.

Increases or decreases in T cell numbers can be observed in blood samples or in samples obtained from thymus, spleen or lymph node tissues. In order to observe the activation of T cells and/or the interaction of T cells and dendritic cells, dendritic cells can be pulsed with antigens ex vivo and then injected into mice to prime CD4+ T cells in draining lymphoid organs. *See* Inaba et al., J. Exp. Med. 172: 631-640, 1990; Liu, et al., J. Exp. Med. 177: 1299-1307, 1993; Sornasse et al., J. Exp. Med. 175: 15-21, 1992. Antigens can also be deposited intramuscularly and dendritic cells from the corresponding afferent lymphatics can carry that antigen in a form stimulatory for T cells. Bujdoso et al., J. Exp. Med. 170: 1285-1302, 1989. According to the invention, factors stimulating the interaction of dendritic cells with T cells in vivo can be identified by administering antigens in this manner and then observing how T cell respond, e.g. by observing whether T cell activation occurs.

Increases or decreases in cytokine levels can be observed by methods provided herein or by other methods available in the art.

Compositions

The CD83 nucleic acids, polypeptides and antibodies of the invention, including their salts, are administered so as to achieve a reduction in at least one symptom associated with an infection, indication or disease.

To achieve the desired effect(s), the nucleic acid, polypeptide or antibody, a variant thereof or a combination thereof, may be administered as single or divided dosages, for example, of at least about 0.01 mg/kg to about 500 to 750 mg/kg, of at least about 0.01 mg/kg to about 300 to 500 mg/kg, at least about 0.1 mg/kg to about 100 to 300 mg/kg or at least about 1 mg/kg to about 50 to 100 mg/kg of body weight, although other dosages may provide beneficial results. The amount

administered will vary depending on various factors including, but not limited to, the nucleic acid, polypeptide or antibody chosen, the disease, the weight, the physical condition, the health, the age of the mammal, whether prevention or treatment is to be achieved, and if the nucleic acid, polypeptide or antibody is chemically modified. Such factors can be readily determined by the clinician employing animal models or other test systems that are available in the art.

Administration of the therapeutic agents in accordance with the present invention may be in a single dose, in multiple doses, in a continuous or intermittent manner, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or prophylactic, and other factors known to skilled practitioners. The administration of the CD83 nucleic acids, polypeptides and antibodies of the invention may be essentially continuous over a preselected period of time or may be in a series of spaced doses. Both local and systemic administration is contemplated.

To prepare the composition, CD83 nucleic acids, polypeptides and antibodies are synthesized or otherwise obtained, purified as necessary or desired and then lyophilized and stabilized. The nucleic acid, polypeptide or antibody can then be adjusted to the appropriate concentration, and optionally combined with other agents. The absolute weight of a given nucleic acid, polypeptide or antibody included in a unit dose can vary widely. For example, about 0.01 to about 2 g, or about 0.1 to about 500 mg, of at least one nucleic acid, polypeptide or antibody of the invention, or a plurality of CD83 nucleic acid, polypeptides and antibodies specific for a particular cell type can be administered. Alternatively, the unit dosage can vary from about 0.01 g to about 50 g, from about 0.01 g to about 35 g, from about 0.1 g to about 25 g, from about 0.5 g to about 12 g, from about 0.5 g to about 8 g, from about 0.5 g to about 4 g, or from about 0.5 g to about 2 g.

Daily doses of the CD83 nucleic acids, polypeptides or antibodies of the invention can vary as well. Such daily doses can range, for example, from about 0.1 g/day to about 50 g/day, from about 0.1 g/day to about 25 g/day, from about 0.1 g/day to about 12 g/day, from about 0.5 g/day to about 8 g/day, from about 0.5 g/day to about 4 g/day, and from about 0.5 g/day to about 2 g/day.

Thus, one or more suitable unit dosage forms comprising the therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention can be administered by a variety of routes including oral, parenteral (including subcutaneous, intravenous, intramuscular and intraperitoneal), rectal, dermal, transdermal, intrathoracic, intrapulmonary and intranasal (respiratory) routes. The therapeutic CD83 nucleic acids, polypeptides or antibodies may also be formulated for sustained release (for example, using microencapsulation, see WO 94/ 07529, and U.S. Patent No.4,962,091). The formulations may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known to the pharmaceutical arts. Such methods may include the step of mixing the therapeutic agent with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if necessary, introducing or shaping the product into the desired delivery system.

When the therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention are prepared for oral administration, they are generally combined with a pharmaceutically acceptable carrier, diluent or excipient to form a pharmaceutical formulation, or unit dosage form. For oral administration, the CD83 nucleic acids, polypeptides or antibodies may be present as a powder, a granular formulation, a solution, a suspension, an emulsion or in a natural or synthetic polymer or resin for ingestion of the active ingredients from a chewing gum. The active CD83 nucleic acids, polypeptides or antibodies may also be presented as a bolus, electuary or paste. Orally administered therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention can also be formulated for sustained release, e.g., the CD83 nucleic acids, polypeptides or antibodies can be coated, micro-encapsulated, or otherwise placed within a sustained delivery device. The total active ingredients in such formulations comprise from 0.1 to 99.9% by weight of the formulation.

By "pharmaceutically acceptable" it is meant a carrier, diluent, excipient, and/or salt that is compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations containing the therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention can be prepared by procedures known in

the art using well-known and readily available ingredients. For example, the nucleic acid, polypeptide or antibody can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, solutions, suspensions, powders, aerosols and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include buffers, as well as fillers and extenders such as starch, cellulose, sugars, mannitol, and silicic derivatives. Binding agents can also be included such as carboxymethyl cellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone. Moisturizing agents can be included such as glycerol, disintegrating agents such as calcium carbonate and sodium bicarbonate. Agents for retarding dissolution can also be included such as paraffin. Resorption accelerators such as quaternary ammonium compounds can also be included. Surface active agents such as cetyl alcohol and glycerol monostearate can be included. Adsorptive carriers such as kaolin and bentonite can be added. Lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols can also be included. Preservatives may also be added. The compositions of the invention can also contain thickening agents such as cellulose and/or cellulose derivatives. They may also contain gums such as xanthan, guar or carbo gum or gum arabic, or alternatively polyethylene glycols, bentones and montmorillonites, and the like.

For example, tablets or caplets containing the CD83 nucleic acids, polypeptides or antibodies of the invention can include buffering agents such as calcium carbonate, magnesium oxide and magnesium carbonate. Caplets and tablets can also include inactive ingredients such as cellulose, pregelatinized starch, silicon dioxide, hydroxy propyl methyl cellulose, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide, benzoic acid, citric acid, corn starch, mineral oil, polypropylene glycol, sodium phosphate, zinc stearate, and the like. Hard or soft gelatin capsules containing at least one nucleic acid, polypeptide or antibody of the invention can contain inactive ingredients such as gelatin, microcrystalline cellulose, sodium lauryl sulfate, starch, talc, and titanium dioxide, and the like, as well as liquid vehicles such as polyethylene glycols (PEGs) and vegetable oil. Moreover, enteric-coated caplets or tablets containing one or more

CD83 nucleic acids, polypeptides or antibodies of the invention are designed to resist disintegration in the stomach and dissolve in the more neutral to alkaline environment of the duodenum.

The therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular, subcutaneous, intraperitoneal or intravenous routes. The pharmaceutical formulations of the therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention can also take the form of an aqueous or anhydrous solution or dispersion, or alternatively the form of an emulsion or suspension or salve.

Thus, the therapeutic CD83 nucleic acids, polypeptides or antibodies may be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion containers or in multi-dose containers. As noted above, preservatives can be added to help maintain the shelve life of the dosage form. The active CD83 nucleic acids, polypeptides or antibodies and other ingredients may form suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active CD83 nucleic acids, polypeptides or antibodies and other ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

These formulations can contain pharmaceutically acceptable carriers, vehicles and adjuvants that are well known in the art. It is possible, for example, to prepare solutions using one or more organic solvent(s) that is/are acceptable from the physiological standpoint, chosen, in addition to water, from solvents such as acetone, ethanol, isopropyl alcohol, glycol ethers such as the products sold under the name "Dowanol," polyglycols and polyethylene glycols, C_1-C_4 alkyl esters of short-chain acids, ethyl or isopropyl lactate, fatty acid triglycerides such as the

products marketed under the name "Miglyol," isopropyl myristate, animal, mineral and vegetable oils and polysiloxanes.

It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes, flavorings and colorings. Antioxidants such as t-butylhydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and a-tocopherol and its derivatives can be added.

Also contemplated are combination products that include one or more CD83 nucleic acids, polypeptides or antibodies of the present invention and one or more other anti-microbial agents. For example, a variety of antibiotics can be included in the pharmaceutical compositions of the invention, such as aminoglycosides (e.g., streptomycin, gentamicin, sisomicin, tobramycin and amicacin), ansamycins (e.g. rifamycin), antimycotics (e.g. polyenes and benzofuran derivatives), β-lactams (e.g. penicillins and cephalosporins), chloramphenical (including thiamphenol and azidamphenicol), linosamides (lincomycin, clindamycin), macrolides (erythromycin, oleandomycin, spiramycin), polymyxins, bacitracins, tyrothycin, capreomycin, vancomycin, tetracyclines (including oxytetracycline, minocycline, doxycycline), phosphomycin and fusidic acid.

Additionally, the CD83 nucleic acids, polypeptides or antibodies are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active nucleic acids, polypeptide or antibody, for example, in a particular part of the intestinal or respiratory tract, possibly over a period of time. Coatings, envelopes, and protective matrices may be made, for example, from polymeric substances, such as polylactide-glycolates, liposomes, microemulsions, microparticles, nanoparticles, or waxes. These coatings, envelopes, and protective matrices are useful to coat indwelling devices, e.g., stents, catheters, peritoneal dialysis tubing, draining devices and the like.

For topical administration, the therapeutic agents may be formulated as is known in the art for direct application to a target area. Forms chiefly conditioned for topical application take the form, for example, of creams, milks, gels, dispersion

or microemulsions, lotions thickened to a greater or lesser extent, impregnated pads, ointments or sticks, aerosol formulations (e.g., sprays or foams), soaps, detergents, lotions or cakes of soap. Other conventional forms for this purpose include wound dressings, coated bandages or other polymer coverings, ointments, creams, lotions, pastes, jellies, sprays, and aerosols. Thus, the therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention can be delivered via patches or bandages for dermal administration. Alternatively, the nucleic acid, polypeptide or antibody can be formulated to be part of an adhesive polymer, such as polyacrylate or acrylate/vinyl acetate copolymer. For long-term applications it might be desirable to use microporous and/or breathable backing laminates, so hydration or maceration of the skin can be minimized. The backing layer can be any appropriate thickness that will provide the desired protective and support functions. A suitable thickness will generally be from about 10 to about 200 microns.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active CD83 nucleic acids, polypeptides or antibodies can also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122; 4,383,529; or 4,051,842. The percent by weight of a therapeutic agent of the invention present in a topical formulation will depend on various factors, but generally will be from 0.01% to 95% of the total weight of the formulation, and typically 0.1-85% by weight.

Drops, such as eye drops or nose drops, may be formulated with one or more of the therapeutic CD83 nucleic acids, polypeptides or antibodies in an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs. Drops can be delivered via a simple eye dropper-capped bottle, or via a plastic bottle adapted to deliver liquid contents dropwise, via a specially shaped closure.

The therapeutic nucleic acids, polypeptide or antibody may further be formulated for topical administration in the mouth or throat. For example, the active ingredients may be formulated as a lozenge further comprising a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the composition in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the composition of the present invention in a suitable liquid carrier.

The pharmaceutical formulations of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and salts of the type that are available in the art. Examples of such substances include normal saline solutions such as physiologically buffered saline solutions and water. Specific non-limiting examples of the carriers and/or diluents that are useful in the pharmaceutical formulations of the present invention include water and physiologically acceptable buffered saline solutions such as phosphate buffered saline solutions pH 7.0-8.0.

The CD83 nucleic acids, polypeptides or antibodies of the invention can also be administered to the respiratory tract. Thus, the present invention also provides aerosol pharmaceutical formulations and dosage forms for use in the methods of the invention. In general, such dosage forms comprise an amount of at least one of the agents of the invention effective to treat or prevent the clinical symptoms of a specific infection, indication or disease. Any statistically significant attenuation of one or more symptoms of an infection, indication or disease that has been treated pursuant to the method of the present invention is considered to be a treatment of such infection, indication or disease within the scope of the invention.

Alternatively, for administration by inhalation or insufflation, the composition may take the form of a dry powder, for example, a powder mix of the therapeutic agent and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges, or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator, insufflator, or a metered-dose inhaler (see, for example, the pressurized metered dose inhaler (MDI) and the dry powder inhaler

disclosed in Newman, S. P. in Aerosols and the Lung, Clarke, S. W. and Davia, D. eds., pp. 197-224, Butterworths, London, England, 1984).

Therapeutic CD83 nucleic acids, polypeptides or antibodies of the present invention can also be administered in an aqueous solution when administered in an aerosol or inhaled form. Thus, other aerosol pharmaceutical formulations may comprise, for example, a physiologically acceptable buffered saline solution containing between about 0.1 mg/ml and about 100 mg/ml of one or more of the CD83 nucleic acids, polypeptides or antibodies of the present invention specific for the indication or disease to be treated. Dry aerosol in the form of finely divided solid nucleic acid, polypeptide or antibody particles that are not dissolved or suspended in a liquid are also useful in the practice of the present invention. CD83 nucleic acids, polypeptides or antibodies of the present invention may be formulated as dusting powders and comprise finely divided particles having an average particle size of between about 1 and 5 μm, alternatively between 2 and 3 μm. Finely divided particles may be prepared by pulverization and screen filtration using techniques well known in the art. The particles may be administered by inhaling a predetermined quantity of the finely divided material, which can be in the form of a powder. It will be appreciated that the unit content of active ingredient or ingredients contained in an individual aerosol dose of each dosage form need not in itself constitute an effective amount for treating the particular infection, indication or disease since the necessary effective amount can be reached by administration of a plurality of dosage units. Moreover, the effective amount may be achieved using less than the dose in the dosage form, either individually, or in a series of administrations.

For administration to the upper (nasal) or lower respiratory tract by inhalation, the therapeutic CD83 nucleic acids, polypeptides or antibodies of the invention are conveniently delivered from a nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to

deliver a metered amount. Nebulizers include, but are not limited to, those described in U.S. Patent Nos. 4,624,251; 3,703,173; 3,561,444; and 4,635,627. Aerosol delivery systems of the type disclosed herein are available from numerous commercial sources including Fisons Corporation (Bedford, Mass.), Schering Corp. (Kenilworth, NJ) and American Pharmoseal Co., (Valencia, CA). For intra-nasal administration, the therapeutic agent may also be administered via nose drops, a liquid spray, such as via a plastic bottle atomizer or metered-dose inhaler. Typical of atomizers are the Mistometer (Wintrop) and the Medihaler (Riker).

Furthermore, the active ingredients may also be used in combination with other therapeutic agents, for example, pain relievers, anti-inflammatory agents, antihistamines, bronchodilators and the like, whether for the conditions described or some other condition.

The present invention further pertains to a packaged pharmaceutical composition for controlling microbial infections such as a kit or other container. The kit or container holds a therapeutically effective amount of a pharmaceutical composition for modulating immune responses and instructions for using the pharmaceutical composition for control of the immune response. The pharmaceutical composition includes at least one nucleic acid, polypeptide or antibody of the present invention, in a therapeutically effective amount such that the selected disease or immunological condition is controlled.

The invention will be further described by reference to the following detailed examples, which are given for illustration of the invention, and are not intended to be limiting thereof.

EXAMPLE 1: Mouse Mutation and Characterization

Mutant Generation

Male C57BL6 mice received 3 weekly injections of N-ethyl-N-nitrosourea (ENU) at a concentration of 100mg/kg. N-Ethyl-N-nitrosourea was quantified prior to injection by spectrophotometry. Mice that regained fertility after a minimum period of 12 weeks were then used to generate pedigree founder G1 animals. G1

male mice were crossed to C57BL6J females and their female progeny (G2 animals) crossed back to their fathers to generate G3 animals for screening.

G3 mice were weaned at 3 weeks of age. Each animal then underwent a series of screens designed to assess a number of parameters, including immune function, inflammatory response and bone development. In the initial screen, conducted at 6 weeks of age, 150-200 µl of whole blood was collected by retro-orbital bleed into heparinized tubes. Cells were pelleted and red blood cells lysed. Samples were then stained with antibodies to cell surface markers expressed on distinct lymphoid and myeloid sub-populations. These samples were analyzed by flow-cytometry.

Mutant Identification

A group of 27 G3 mice from 2 different pedigrees, pedigree 9 and pedigree 57 (i.e. derived from 2 distinct G1 fathers) were analyzed in this screen. Two animals from pedigree 9 were identified as having a reduced (>2 standard deviation from normal) percentage of CD4+ T cells in peripheral blood (Figure 1). Both animals were descended from the same G1 and shared the same mother. All other animals screened on that day had a normal percentage of CD4+ T cells. The number of phenodeviants identified (2 from a litter of 9 animals) was suggestive of a trait controlled by a single gene and inherited in a Mendelian fashion.

A second litter generated from Pedigree 9 bred to G2 daughter #4 exhibited an identical phenotype with reduced numbers of CD4+ T cells, further suggesting that the trait had a genetic basis. The phenotype was designated LCD4.1 (Low CD4 Mutant # 1) and was used for mapping experiments.

Mutation Mapping

In order to map the LCD4.1 mutant phenotype, affected G3 male mice (presumptive homozygous for the mutation) were bred to female animals from the C3HeB/FeJ strain to generate F1 progeny. These F1 females (presumptively heterozygous for the mutation) were then mated back to their affected father to generate N2 progeny.

Blood was collected from N2 animals and flow cytometric analysis was performed to identify CD4+ T cells. For a phenotype controlled by a single gene, breeding homozygous fathers to heterozygous daughters should yield 50% normal N2 animals and 50% affected N2 animals. This ratio of normal to affected animals was observed in the N2 generation: Multiple N2 animals exhibited a reduced percentage of CD4+ T cells, indicating that the phenotype was heritable (Figure 2).

DNA samples were prepared from samples of tail tissue collected from these N2 mice and used for a genome scan, using a collection of assembled markers, and performed on the ABI 3100 DNA analyzer. Initial genetic linkage was seen to the tip of chromosome 13, where the closest microsatellite marker was D13Mit139 with a LOD score of 8.2. By calculating upper and lower confidence limits, the mutant gene was located between 13.4 and 29.6 cM on chromosome 13. Through additional genotyping, this region was reduced to an 11 cM interval on chromosome 13. No significant linkage to other chromosomal regions was seen.

Mutation Identification

A candidate gene, CD83, was identified for gene-testing based upon its reported position within the interval. CD83 has previously been used as a marker of dendritic cell activation, suggesting that it might play a role in dendritic cell function and hence in regulating T cell development and function.

Sequence analysis of the mutant DNA revealed a mutation in the stop codon of CD83. All affected animals were homozygous for this mutation while non-affected animals carried one wild-type allele and one mutant allele (Figure 3 and Figure 4). The mutation destroyed the stop codon and resulted in the addition of a unique 55 amino acid tail to the C-terminus of CD83 (Figure 5).

Additional Functional Data

A reduction in CD4+ T cells was seen in peripheral blood, spleen tissues and lymph nodes from homozygous LCD4.1 mice. Although there were a reduced number of CD4+ T cells in the thymus there is no overt block in the developmental process and there was substantially no alteration in B cell development in the bone

marrow. Histological evaluation of thymus, spleen and lymph nodes from affected mice revealed no gross alteration in tissue architecture.

Dendritic cells can be differentiated from bone marrow of wild type mice by culture in GM-CSF. These cells can be characterized by the surface expression of dendritic cell markers, including CD86 and CD11c. Both LCD4.1 affected and normal animals were capable of giving rise to CD86+CD11c+ cells under these culture conditions. LCD4.1 mutant mice thus were capable of generating dendritic cells under *in vitro* culture conditions. These data suggest that the phenotype seen in LCD4.1 mice is not due to a failure of dendritic cells to develop but rather may reflect a defect in function.

To track dendritic cells, the sensitizing agent FITC was applied to the dorsal surface of the ears of LCD4.1 affected and wild-type mice. FITC was picked up by dendritic cells that then migrated to the draining auricular lymph nodes, where the presence of the FITC label on the dendritic cell surface permitted detection by flow-cytometry. FITC labeled cells expressing CD86 were detected in equal proportions in draining lymph node from normal and affected LCD4.1 mice. These data indicate that LCD4.1 mutant animals are capable of generating dendritic cells in vivo and that these cells are able to pick up antigen in the ear and travel to the draining lymph node.

EXAMPLE 2: CD83 and CD4+ T Cell Function

Materials and Methods

Spleens were removed from wild type and mutant mice and digested with collagenase to liberate dendritic cells. Spleens were stained for surface expression of CD4 (helper T cells) and CD11c (dendritic cells). Cells expressing these markers were purified by fluorescence activated cell sorting (FACS sorting). CD11c and CD4+ positive cells were also purified from an allogeneic mouse strain, BALBc.

Mixed lymphocyte cultures were set up using purified cell populations. Dendritic cells from BALBc animals were used to stimulate CD4+ T cells from wild type and mutant mice. In a reciprocal experiment dendritic cells prepared from wild

type and mutant mice were used to stimulate BALBc CD4+ T cells. After 5 days in culture proliferative responses were measured by incorporation of tritiated thymidine.

Dendritic cells from wild type and mutant mice were both capable of activating allogeneic T cells, suggesting that dendritic cell function was unimpaired in the mutant animal (Figure 6a). In contrast CD4+ T cells from mutant animals exhibited a diminished response after 5 days of stimulation (Figure 6b).

These data suggest that the mutation in the CD83 gene has minimal effect on dendritic cells intrinsic function but rather has a profound effect upon T cell activity. The CD4+ T cell therefore may have a novel requirement for CD83 functionality on T cells during allogeneic activation. CD83 may be influencing the extent of CD4+ T cell activation or altering the duration of the CD4+ T cell proliferative response. The therapeutic manipulation of CD83 may thus represent a mechanism for the specific regulation of T cell function in the treatment of T cell mediated diseases, including autoimmune disorders. Antibodies capable of blocking CD83 function may be used as therapeutics in the treatment of immune diseases whilst the activation of CD83 may have utility in enhancing immune responses in cancer and other circumstances.

Conclusion

Although CD83 has been described as a marker of dendritic cell activation there has previously been little data describing its function *in vivo*. However, the mutation provided by the invention destabilizes or inactivates the protein and leads to impaired surface expression. As a consequence, CD4+ T cell function is impaired. However, the development of dendritic cells is not inhibited and mutant dendritic cells retain functionality. Nonetheless, the result is impaired development of CD4+ T cells. This impaired ability to activate T cells is also seen in a slight decrease in contact sensitivity responses in LCD4.1 mutant mice.

EXAMPLE 3: Mutant CD83 Have Different Cytokine Levels than Wild Type Mice

This Example demonstrates that $CD4^+$ T-cells from CD83 mutant animals express higher levels of IL-4 and lower levels of IL-2 compared to $CD4^+$ T-cells from CD83 wild type animals.

Methods for cell activation and cytokine measurements:

Spleens cells from 6-8-week-old homozygous CD83 wild type or CD83 mutant (LCD4.1) mice were used to isolate $CD4^+$ T-cells by positive selection using magnetic beads (Miltenyi Biotec). A 96 round bottom plate was coated with 50μL per well of a solution containing either 1 or 10 μg/mL of anti-CD3 and 0.1 or 0.2 μg/mL of anti-CD28 antibodies (both from Pharmingen) in PBS overnight. This plate was then washed using 150 μL of PBS three times. To this pre-coated plate, 20,000 $CD4^+$ T-cells (either wild type or CD83 mutant) were added in a 200 μL final volume of RPMI containing 10% FBS, 55 μM ß-mercaptoethanol and antibiotics. The plates were then incubated in a CO_2 incubator at 37 °C for 44 to 72 hours. For determination of cytokine levels, supernatants were harvested and cytokines were measured using either a Cytometric Bead Array system (Pharmingen) or ELISA (R&D). For RNA measurements, the cells were harvested and RNA was isolated using Tri reagent (Sigma). IL-10 and IL-4 mRNA levels were measured by reverse transcription and TaqMan (Applied Biosystems) analysis.

Results:

Figure 7 shows the IL-2, IL-4, IL-5, TNFa and IFN? levels produced by either wild type or CD83 mutant $CD4^+$ T-cells. Purified cells were incubated as described above in the presence of 1μg/mL of anti-CD3 and 0.2 μg/mL of anti-CD28 antibodies for 72 hours. The supernatants were then simultaneously analyzed for production of IL-2, IL-4, IL-5, TNFa and IFN? using the cytometric bead array system from Pharmingen.

Figure 7 demonstrates that $CD4^+$ T-cells from CD83 mutant animals expressed higher levels of IL-4 and lower levels of IL-2 compared to $CD4^+$ T-cells

from CD83 wild type animals. Other cytokines and a new set of stimulation assays were analyzed including the production levels of IL-10 and GMCSF by these cells (Figures 8 and 9). In both cases, cells from mutant animals produce larger amounts of IL-10 and GMCSF than did wild type animals. Figure 10 shows that mRNA levels for both IL-4 and IL-10 were increased in cells from activated mutant CD83, $CD4^+$ T-cells compared with cells from wild type animals.

EXAMPLE 4: Anti-CD83 Antibodies Mimic the Effects of the CD83 Mutation

Methods for antibody testing:

For modulation of cytokine production by anti-CD83 antibodies, $CD4^+$ T-cells were isolated and activated as described above. Activation was performed in the presence of increasing concentrations of anti-CD83 antibodies. For proliferation assays, $CD4^+$ T-cells were isolated from an OT2tg mouse. OT2tg mice are transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide. Dendritic cells were isolated from a C57BL6 mouse by a negative selection using B220 magnetic beads (Miltenyi Biotec) followed by positive selection using CD11-c magnetic beads (Milteny Biotec). Five thousand $CD4^+$ T-cells were then mixed with five thousand dendritic cells in a 96 well plate in the presences of 1 μM OVA peptide using RPMI (55 μM BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO_2 incubator at 37°C and pulsed using [^{3}H] thymidine for 8 hours. Cells were then harvested and [^{3}H] thymidine incorporation was quantified using a top counter.

Results:

In some assays, anti-CD83 antibodies decreased production of IL-4 by activated $CD4^+$ T-cells in a dose dependent manner. Different antibody preparations did provide somewhat different degrees of inhibition of IL-4 production (Figure 11). Accordingly, the epitope and/or degree of affinity of the

antibodies for the CD83 antigen may influence whether or not IL-4 production is significantly inhibited.

The effects of anti CD83 antibodies on proliferation of a peptide specific T-cell proliferation assay using the OT2 T-cell receptor (TCR) transgenic system were also observed. $CD4^+$ T-cells derived from these TCR transgenic animals express high levels of a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide and thus have high levels of proliferation when mixed with antigen presenting cells (dendritic cells were used) in the presence of the OVA peptide. In such assays, anti-CD83 antibodies were able to decrease proliferation of $CD4^+$ T-cells in this system (Figure 12). However, different antibody preparations had somewhat different effects on the proliferation of $CD4^+$ T-cells. Accordingly, the CD83 epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not $CD4^+$ T-cell proliferation is significantly inhibited.

EXAMPLE 5: Increased T-Cell Proliferation by Transgenic Expression of CD83

This Example illustrates that over expression of CD83 in transgenic mice leads to increased T-cell proliferation.

Materials and Methods

A 34.3 kb fragment of normal mouse genomic DNA, including the ~18 kb coding region of the CD83 gene, as well as ~10.6 kb of upstream flanking sequences and ~5.7 kb of downstream sequences was microinjected into normal mouse one-cell embryos. Four individual founder animals were generated. Transgenic mice were then crossed to a male OT2tg mouse. Male offspring carrying both the CD83 and OT2 transgene were used to analyze peptide specific T-cell proliferation.

For proliferation assays, $CD4^+$ T-cells and dendritic cells were isolated from either OT2tg [transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide] CD83 wild type or from OT2tg CD83 transgenic mice as

described above (Example 4). Five thousand OT2tg $CD4^+$ T-cells from either wild type or CD83 transgenic animals were then mixed with five thousand wild type dendritic cells or five thousand CD83 transgenic dendritic cells in a 96 well plate in the presence of increasing concentrations of OVA peptide using RPMI (55 μM BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO_2 incubator at 37C and pulsed using [^{3}H] thymidine for 8 hours. Cells were then harvested and [^{3}H] thymidine incorporation was quantified using a top counter.

Results:

OT2tg $CD4^+$ T-cells derived from CD83 transgenic mice proliferated at higher rates than the same cell population derived from a CD83 wild type animal (Figure 13). This increased proliferation was seen at all the concentrations of OVA peptide tested. Whereas OT2tg $CD4^+$ T-cells derived from CD83 transgenic animals exhibited increased proliferation, dendritic cells from CD83 transgenic animals did not exhibit a substantial increase in proliferation. Therefore, it appears that transgenic expression in the $CD4^+$ T-cell, and not in dendritic cells is what led to the increased proliferation of $CD4^+$ T-cells.

EXAMPLE 6: Inhibition of proliferation of PHA activated human PBMCs by protein A purified rabbit anti-mouse CD83 antibodies

This Example shows that antibodies raised against the CD83 protein can inhibit proliferation of human peripheral blood mononuclear cells.

Materials and Methods

Rabbit polyclonal sera was raised against mouse CD83 protein by immunizing rabbits using a mouse CD83 external domain protein fused to a rabbit Ig domain (Figure 14). Pre-immune sera and anti-mouse polyclonal sera were then purified using a protein A column (Pharmacia Biotech) as described by the

manufacturer, then dialyzed against PBS and stored at 4° C. To monitor the recognition of mouse CD83 protein by the polyclonal sera, which was obtained at different dates post immunization, a titer was obtained using an antigen specific ELISA (Figure 15). As illustrated by Figure 15, a good polyclonal response was obtained against the mouse CD83 protein.

Human peripheral blood mononuclear cells (PBMCs) were isolated using a Ficoll gradient (Ficoll Paque Plus, Pharmacia) and washed with PBS buffer. For activation and proliferation studies, five thousand cells were incubated in 200 μL of media (RPMI, 10%FBS, antibiotics) and 5ug/mL of *Phaseolus vulgaris* leucoagglutinin (PHA) in the presence or absence of increasing concentrations of Protein A purified pre-immune sera or with similarly purified anti-CD83 polyclonal antibodies. After 48 hours at 37°C in a CO_2 incubator the cells were pulsed with [^{3}H] thymidine for ~8 hours and harvested. Thymidine incorporation into the PBMCs was measured using a top counter for analysis.

A Selected Lymphocyte Antibody Method (SLAM) procedure was used to establish monoclonal antibody cell lines from the rabbits used to generate the anti-CD83 antibodies. Antibody forming cells were isolated from the immunized rabbits that produced antibodies capable of binding CD83, the genes encoding antibodies that recognized CD83 and inhibited proliferation of lymphocytes were then cloned by PCR amplification and sequenced. Separate lines of monoclonal antibody producing cells were then established and expanded in culture. Antibodies were purified using Protein A chromatography according to manufacturer's instructions and tested for their ability to recognize CD83 proteins and to inhibit proliferation of PHA stimulated human PBMCs.

Results

Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by polyclonal antibodies raised against the external region of the mouse CD83 protein. Proliferation of PHA-activated human PBMCs was not affected by addition of increasing concentrations of protein A purified rabbit pre-immune sera. When increasing concentrations of protein A purified rabbit polyclonal sera raised

against the mouse CD83 protein was added, a concentration dependent decrease in proliferation was observed.

These data indicate that antibodies raised against the mouse protein are able to cross-react with the human protein. Moreover, antibodies raised against the mouse protein are able to inhibit proliferation of PHA-activated human PBMCs.

A summary of the characteristics of two monoclonal antibody preparations having functional activity is shown in Table 1. Isolated recombinant mouse and human CD83 protein preparations were used for the BIACORE and ELISA assays. Endogenous human CD83 protein expressed in a human KMH2 cell line was used for FACS assays.

Table 1 – Monoclonal Antibody Functionality and Reactivity with Mouse and Human CD83

Assay	95F04 Antibodies	96G08 Antibodies
Inhibition of human PBMC proliferation	++	+++
Biacore – mouse CD83	+++	+++
Biacore – human CD83	++	–
ELISA – mouse CD83	+++	+++
ELISA – human CD83	++	–
FACS – human CD83	ND	++

ND: not determined

While the 96G08 antibodies appeared to have reduced affinity for human CD83 protein via the Biacore and ELISA assays, the FACS assay indicated that this antibody preparation could bind to endogenously produced human CD83 (Figures 18 and 19). Moreover, the 96G08 antibodies were able to inhibit proliferation of human peripheral blood mononuclear cells (PBMCs), as illustrated in Figure 20. Hence, some aspect of either the purification or the structure of the isolated recombinant human protein may have influenced the in vitro binding of 96G08 antibodies to the recombinant human CD83. For example, the recombinant human CD83 protein employed for the Biacore and ELISA assays is a chimeric protein that is joined to a portion of an immunoglobulin Fc fragment. Removal of this Fc fragment may improve in vitro binding to the human CD83 protein.

Figure 20 illustrates that the 95F04 and 96G08 antibody preparations can inhibit proliferation of PHA activated human peripheral blood mononuclear cells as

detected by incorporation of [^{3}H] thymidine. As shown, when no antibody was present about 10,000 cpm of [^{3}H] thymidine was incorporated into human peripheral blood mononuclear cells. However, when 30 μg/ml of the 95F04 antibody preparation was present, incorporation of [^{3}H] thymidine dropped to about 2000 cpm. The 96G08 antibody preparation had an even greater effect on [^{3}H] thymidine incorporation. When 30 μg/ml 96G08 antibody preparation was added to human peripheral blood mononuclear cells, [^{3}H] thymidine incorporation was reduced to about 300 cpm. These data indicate that the 95F04 and 96G08 antibody preparations can alter the function of human CD83 *in vitro*.

EXAMPLE 7: Multimerized Anti-CD83 Antibodies Inhibit Proliferation of Immune Cells

This Example shows that antibodies raised against the CD83 protein as described in the previous example are particularly effective at inhibiting proliferation of immune cells after the antibodies are multimerized or multimerized by binding the antibodies to a solid support or by cross-linking in solution.

Materials and Methods

Round bottom microtiter plates were coated with different preparations of anti-CD83 antibody preparations by incubating the plates with 50 μl of 50 μg/ml antibody preparation per well either for 2 hours at 37 °C or overnight at 4 °C. As a positive control, some wells were coated with anti-LFA antibodies that are known to inhibit proliferation of lymphocytes. After coating, the wells were then washed thoroughly with PBS.

Mouse (C57B16) spleen cells were isolated and plated in the antibody or control treated wells at 30,000 cells per well. For activation, Concavalin A was added to a final concentration of 1.0 μg/ml. Cellular proliferation was assessed by measuring the incorporation of tritiated thymidine during the last 6 to 8 hours of a 48 hour incubation. In another experiment, the specificity of the observed antibody-

induced inhibition of lymphocyte proliferation was tested by repeating this experiment with addition of mouse CD83 protein before adding the lymphocytes to the antibody coated microtiter wells.

As described in more detail below, the 6G05 antibody preparation was identified as a good inhibitor of lymphocyte proliferation. In contrast, the 112D08 antibody preparation was identified as having little or no inhibitory activity when bound to microtiter wells. The 112D08 antibody preparation was used as a negative control in some of the subsequent experiments.

The inhibitory activities of plate-bound versus soluble, cross-linked 6G05 antibodies were compared in another experiment. Plate-bound 6G05 antibodies were prepared as described above. Approximately 30,000 activated lymphocytes were added per well to antibody coated plates or to non-coated plates containing 1.0 or 5.0 μg/ml soluble 6G05 antibody preparation. A secondary rabbit anti-mouse antibody (10 μg/ml or 25 μg/ml) was added to the wells containing the soluble 6G05 antibody preparation to act as a cross-linking reagent for the 6G05 antibodies. Cellular proliferation was assessed by incorporation of tritiated thymidine as described above.

Results

The results of one screen for anti-CD83 antibody preparations that can inhibit lymphocyte proliferation are shown in Figure 25A-B. As illustrated in Figure 25A many anti-CD83 antibody preparations inhibit proliferation of activated lymphocytes, including the 94c09, 98a02, 94d08, 98d11, 101b08, 6g05, 20d04, 14c12, 11g05, 12g04, 32f12 and 98b11 preparations. Note that some variation in the degree of inhibition obtained is observed. For example, while the 98b11 preparation is not so effective, the 6g05 antibody preparation is a highly effective inhibitor of lymphocyte proliferation.

Figure 25B further illustrates that some antibody preparations are highly effective inhibitors (e.g. 117G12) but others are not (e.g. 98g08). The 824pb antibody refers to rabbit polyclonal antisera; as shown this polyclonal antisera was not particularly effective at inhibiting lymphocyte proliferation

Figure 26 illustrates that the inhibitory activity of the 6g05 antibody preparation is quenched by soluble mouse CD83 protein. In this assay, mouse CD83 protein was added to anti-CD83 antibody-coated wells before activated lymphocytes were introduced. Both a highly effective proliferation inhibitor (6g05) and an antibody preparation with little or no inhibitory activity (98g08) were tested. A control having no antibody and no mouse CD83 protein as well as a control with added mouse CD83 and no antibody was included. Cellular proliferation of the activated lymphocytes was assessed by observing the incorporation of tritiated thymidine as described above. As shown in Figure 26, the 6g05 antibody strongly inhibits lymphocyte proliferation when no mouse CD83 is present. However, when mouse CD83 is added before the lymphocytes, the 6g05 antibody exhibits little or no inhibition of lymphocyte proliferation. These data indicate that the inhibitory activity of the 6g05 antibody preparation operates through the CD83 gene product, rather than through some non-specific interaction with lymphocytes.

Figures 27 and 28 illustrate that anti-CD83 antibodies that are multimerized by use of a rabbit anti-mouse antibody have inhibitory activity that is like that of plate-bound anti-CD83 antibodies. The proliferation of lymphocytes was measured by observing the incorporation of tritiated thymidine with and without anti-CD83 antibodies as described above. In one set of assays plate-bound 6g05 antibodies were used and in another soluble 6g05 antibodies were employed. The soluble 6g05 antibodies were cross-linked by addition of rabbit anti-mouse antibodies that bind to the Fc region of the 6g05 antibodies. For comparison, a soluble and plate-bound antibody preparation with no inhibitory activity (the 112D08 antibody preparation was also tested. A similar series of assays were set up using a panel of soluble anti-CD83 antibodies.

As shown in Figure 27, both plate-bound and crosslinked 6g05 antibodies were highly effective inhibitors of lymphocyte proliferation. These data indicate that the method of aggregating anti-CD83 antibodies is not particularly important. In other words the multimerization can be achieved by adhering or attaching antibodies to a solid support or by crosslinking the anti-CD83 antibodies through their Fc regions using a rabbit anti-mouse secondary antibody. So long as the anti-

CD83 antibodies are in close proximity, they are effective inhibitors of lymphocyte proliferation.

Figure 28 shows that many soluble anti-CD83 antibodies exhibit good inhibition of lymphocyte proliferation when they are cross-linked with the rabbit anti-mouse secondary antibody. For example, the 6g05, 11g04, 12g04, 14c12, 20d04, 32f12, 94c09, 94d08, 98a02, 98d11(3), 101B08(2.7) and 117g12 antibody preparations strongly inhibit lymphocyte multimerization when cross-linked with the rabbit anti-mouse antibodies.

EXAMPLE 8: Multimerized Anti-CD83 Antibodies Inhibit Proliferation of Immune Cells in a Mixed Lymphocyte Reaction

This Example shows that multimerized anti-CD83 antibodies inhibit proliferation of lymphocytes in a mixed lymphocyte reaction (MLR) assay.

Materials and Methods

The MLR assay employed was a modification of the procedure described in Bradley, pp 162-166 in Mishell et al., eds. Selected Methods in Cellular Immunology (Freeman, San Francisco, 1980); and Battisto, et al., Meth, in Enzymol. 150:83-91 (1987).

Spleens were removed from BALBc and C57B16 mice and digested with collagenase to liberate dendritic and $CD4^+$ cells, respectively. Spleens were stained for surface expression of CD4 (helper T cells) or CD11c (dendritic cells). Cells expressing these markers were purified by using magnetic beads (Miltenyi) according to the manufacturer's instructions.

Mixed lymphocyte cultures were set up using purified cell populations. Plates with different anti-CD83 antibody preparations bound thereto were prepared as described in the previous examples. Approximately 1250 CD11c dendritic cells were used to stimulate approximately 20,000 CD4+ T cells. After 4 days in culture, proliferative responses were measured by incorporation of tritiated thymidine. A positive control antibody, the anti-LFA antibody, was also used for comparison

purposes in this assay because it is known to inhibit lymphocyte proliferation in MLR assays.

A similar experiment was performed to assess the recall response of lymphocytes exposed to 100 μg/ml anti-CD83 antibodies. Prior to spleen removal and CD11c and CD4+ cell isolation, BALBc mice were first immunized with keyhole limpet hemocyanin (KLH) in a 1:1 ratio with complete Freund's adjuvant close to the lymph node area. Lymph nodes were harvested and challenged in vitro with KLH at a final concentration of 2.5 μg/ml and the proliferative response of the cells was assayed as described above by observing incorporation of tritiated thymidine.

Results

Figure 29 shows that the conditions employed several monoclonal anti-CD83 antibodies can inhibit lymphocyte proliferation in a mixed lymphocyte reaction assay. For example, the 98a02, 98d11, 20d04, 14c12, 12g04, and 117g12 inhibit lymphocyte proliferation in this assay.

Figure 30 shows that many anti-CD83 antibody preparations can inhibit the recall response of lymphocytes. For example, 94c09, 98a02, 6g05, 20d04, and 117104 antibody preparations inhibited proliferation of activated lymphocytes exposed to an antigen (KLH) to which they had been immunized.

These data suggest that anti-CD83 antibodies can quiet the proliferative response of CD4+ T cells after stimulation by allogenic CD11 cells and/or antigen.

EXAMPLE 9: Exposure to Anti-CD83 Antibodies Does Not Cause Apoptosis of Activated Lymphocytes

This Example shows that exposure to anti-CD83 antibodies does not lead to apoptosis of activated lymphocytes.

Materials and Methods

Mouse (C57B16) spleen cells were isolated and activated by incubation for

24 hours with 1.0 μg/ml Concavalin A in the presence or absence of anti-CD83 antibodies and rabbit anti-mouse antibodies as a crosslinking reagent as described above. Cells were incubated for 48 hours at 37 °C. Proliferative responses were measured by incorporation of tritiated thymidine. Total caspase activity and annexinV expression levels were used as a measure of apoptosis.

Homogeneous total caspase activity was measured using a kit (Roche(following the manufacturer's instructions.

To test for apoptosis using annexinV expression, cells were incubated with annexin-FITC and propidium iodide (AnnexinV-FITC kit, Calbiochem) and the percentage of positive Annexin V-FITC labeled cells was determined by Fluorescence Activated Cell sorting (FACs).

Results

Figure 31A-B shows that soluble but cross-linked 6g05 and 14c12 anti-CD83 antibody preparations not only inhibit activated lymphocyte cell proliferation (Figure 31B) but also have very low caspase activity (Figure 31A). Similarly, Figure 32 shows that the percentage of activated lymphocytes that express annexinV is reduced after treatment with soluble but cross-linked 6g05 and 14c12 anti-CD83 antibody preparations.

These data indicate that while anti-CD83 antibodies inhibit proliferation of ConA activated splenocytes, they do not induce apoptosis of immune cells. Instead, anti-CD83 antibodies actually depress the expression of apoptosis markers. Hence, the reduction in cell proliferation observed when activated lymphocytes are exposed to anti-CD83 antibodies is not due to increased programmed cell death.

EXAMPLE 10: Exposure to Anti-CD83 Antibodies Does Not Inhibit Activation of Lymphocytes

This Example shows that exposure to anti-CD83 antibodies does not inhibit activation of lymphocytes.

Materials and Methods

Mouse (B6) spleen cells were isolated and activated using Concavalin A as described above in the presence or absence of anti-CD83 antibodies and the secondary anti-mouse crosslinking antibodies. The anti-CD83 antibody preparations employed included the 6g05, 14c12, 98b11 and 112d08 preparations. Activation of the cells was assessed using CD69 expression as a marker of cell activation.

Results

Figure 33 illustrates that splenocytes activated with Concavalin A express the CD69 activation marker even though they were incubated with anti-CD83 antibodies. In particular, the star or asterisks in the lower right hand corner of the graph shows the level of CD69 expression observed when splenocytes are not activated with Concavalin A. However, when splenocytes were activated with Concavalin A they expressed high levels of CD69 even after incubation with any of the 6g05, 14c12, 98b11 or 112d08 anti-CD83 antibody preparations.

These results indicate that while cellular proliferation of lymphocytes exposed to anti-CD83 antibodies is arrested, the lymphocytes still undergo activation.

EXAMPLE 11: Anti-CD83 Antibodies Arrest the Lymphocyte Cell Cycle in the G0/G1 Stage

This Example shows that exposure to anti-CD83 antibodies arrests activated lymphocytes in the G0/G1 stage of the cell cycle.

Materials and Methods

Mouse (B6) spleen cells were isolated and activated by incubation for 48 hours with 1.0 μg/ml Concavalin A in the presences of anti-CD83 antibodies with the crosslinking antibodies as described above. To analyze cell cycle distribution, cells were fixed and DNA was stained with propidium iodine according to the

protocol described for the flowcytometer (Cold Spring Harbor, NY). WinMDI software was used for background subtraction caused by debris in the DNA histogram. Each histogram was further analyzed by cycle red software to obtain the distribution of cells therein. In addition, the size and shape of the activated cells was assessed by their forward (FSC) and side (SSC) scatter during this experiment.

The anti-CD83 antibody preparations employed were the 6g05 and 14c12 preparations that had been shown to inhibit cellular proliferation and the 112d08 preparation that had little or no effect on cellular proliferation. Cells having 2N complement of DNA were assumed to be in the G1/G0 phase of the cell cycle; cells having 3N complement of DNA were assumed to be in the G2/M phase of the cell cycle; and cells having 4N complement of DNA were assumed to be in the S phase of the cell cycle. The percentage of cells having G1/G0, G2/M or S phase of the cell cycle was determined and plotted in Figure 35A-C.

Results

Figure 34 shows that a population of activated splenocytes mixed with anti-CD83 antibody preparations have lost the blasting (dividing) cells as detected by FACS sorting. Almost all cells sort as small cells with a 2N content of DNA as illustrated by the high proportion of cells towards the left (smaller) side of the population distribution in Figure 34.

Figure 35A-C show that treatment of Concavalin A activated lymphocytes with either of 6g05 and 14c12 antibody preparations leads to a cellular population that was enriched in cells in the G1/G0 stage of the cell cycle. Treatment with either the rabbit anti-mouse antibody or the 112d08 antibody preparation that has little or no effect on cell proliferation did not lead to a cellular population that was enriched in cells in the G1/G0 stage of the cell cycle.

These data indicate that exposure to anti-CD83 antibodies arrests lymphocytes in the G1/G0 stage. Taken together with the data in preceding Examples, these data indicate that anti-CD83 antibodies can cause lymphocytes to enter a state of antigen specific unresponsiveness or anergy.

All patents and publications referenced or mentioned herein are indicative of the levels of skill of those skilled in the art to which the invention pertains, and each such referenced patent or publication is hereby incorporated by reference to the same extent as if it had been incorporated by reference in its entirety individually or set forth herein in its entirety. Applicants reserve the right to physically incorporate into this specification any and all materials and information from any such cited patents or publications.

The specific methods and compositions described herein are representative of preferred embodiments and are exemplary and not intended as limitations on the scope of the invention. Other objects, aspects, and embodiments will occur to those skilled in the art upon consideration of this specification, and are encompassed within the spirit of the invention as defined by the scope of the claims. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any element or elements, or limitation or limitations, which is not specifically disclosed herein as essential. The methods and processes illustratively described herein suitably may be practiced in differing orders of steps, and that they are not necessarily restricted to the orders of steps indicated herein or in the claims. As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality (for example, a culture or population) of such host cells, and so forth. Under no circumstances may the patent be interpreted to be limited to the specific examples or embodiments or methods specifically disclosed herein. Under no circumstances may the patent be interpreted to be limited by any statement made by any Examiner or any other official or employee of the Patent and Trademark Office unless such statement is specifically and without qualification or reservation expressly adopted in a responsive writing by Applicants.

The terms and expressions that have been employed are used as terms of description and not of limitation, and there is no intent in the use of such terms and

expressions to exclude any equivalent of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention as claimed. Thus, it will be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

Other embodiments are within the following claims. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.